

A STUDY OF SERUM MAGNESIUM LEVEL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Dissertation submitted for

Branch I – MD (GENERAL MEDICINE)

April 2015



THE TAMILNADU Dr. M.G.R. MEDICAL
UNIVERSITY, CHENNAI, TAMILNADU.

CERTIFICATE

This is to certify that the dissertation entitled “**A STUDY OF SERUM MAGNESIUM LEVEL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS**” is the bonafide work of **Dr.V.PRAVEEN** in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine Branch I examination to be held in **April 2015**.

Dr.S.VADIVEL MURUGAN MD.,

Professor and HOD,
Department of Medicine,
Government Rajaji Hospital,
Madurai Medical College,
Madurai.

Dr.R.BALAJINATHAN MD.,

Professor,
Department of Medicine
Government Rajaji Hospital,
Madurai Medical College,
Madurai.

**Capt.Dr.B.SANTHAKUMAR M.Sc(F.Sc),
M.D(F.M),PGDMLE,Dip.N.B(F.M),,**

Dean

Government Rajaji Hospital,
Madurai Medical College,
Madurai.

DECLARATION

I, **Dr.V.PRAVEEN**, solemnly declare that, this dissertation “**A STUDY OF SERUM MAGNESIUM LEVEL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS**” is a bonafide record of work done by me at the Department of General Medicine, Government Rajaji Hospital, Madurai, under the guidance of **Dr.R.BALAJINATHAN M.D.**, Professor, Department of General Medicine, Madurai Medical college, Madurai. This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulations for the award of Degree of Doctor of Medicine (M.D.), General Medicine Branch-I, examination to be held in April 2015.

Place: Madurai

Date:

Dr.V.PRAVEEN

ACKNOWLEDGEMENT

I would like to thank **Capt.Dr.B.SANTHAKUMAR M.Sc(F.Sc), M.D(F.M),PGDMLE,Dip.N.B(F.M).**, Dean, Madurai Medical College, Madurai, for permitting me to utilise the hospital facilities for dissertation.

I also extend my sincere thanks and gratitude to **Prof.Dr.S.VADIVELMURUGAN MD**, The Head of the Department and the Professor of Medicine for his constant support during the study.

I would like to express my deep sense of gratitude and thanks to my Unit Chief, my guide and the Professor of Medicine, **Dr.R.BALAJINATHAN MD.**, for his valuable suggestions and excellent guidance during the study. I am greatly indebted to my beloved Professors, **Dr.V.T.PREMKUMAR, M.D., Dr.M.NATARAJAN, M.D., Dr.G.BAGHYALAKSHMI, M.D., Dr.J.SANGUMANI, M.D., Dr.C.DHARMARAJ, M.D., and Dr.R.PRABHAKARAN, M.D.**, for their valuable suggestions throughout the course of study.

I would also like to thank **Dr. P.MOHAN KUMARESH MD.**, professor and HOD; Department of Biochemistry for his valuable advice and support during the study.

I thank the Assistant Professors, **Dr.G.GURUNAMASIVAYAM MD., Dr.V.N.ALAGAVENKATESAN MD., Dr.L.VELUSAMY MD.,** for their valid comments, guidance and suggestions.

I wish to acknowledge all those, including my post graduate colleagues, my parents who have directly or indirectly helped me complete this work with great success.

Last but definitely not the least, I thank all the patients who participated in this study for their extreme patience and co-operation without whom this project would have been a distant dream and I pray God, for their speedy recovery.

CONTENTS

S.NO	CONTENTS	PAGE NO
1	INTRODUCTION	01
2	AIM OF STUDY	03
3	REVIEW OF LITERATURE	04
4	MATERIALS AND METHODS	79
5	RESULTS AND INTERPRETATION	83
6	DISCUSSION	95
7	CONCLUSION	99
8	SUMMARY	100
9	ANNEXURES	101
	BIBLIOGRAPHY PROFORMA ABBREVIATIONS MASTER CHART ETHICAL COMMITTEE APPROVAL LETTER ANTI PLAGIARISM CERTIFICATE	

A STUDY OF SERUM MAGNESIUM LEVEL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

ABSTRACT:

Type 2 diabetes mellitus constitutes around 80 to 95 % of adult onset diabetes. Hypomagnesemia is associated with type 2 diabetes but a significant proportion of population suffering from this metabolic disorder is not aware about it. This study was conducted in the General Medicine OPD, Government Rajaji Hospital, Madurai from April 2014 to September 2014 to measure the serum magnesium level in type 2 diabetes patients. A total of 200 subjects were selected, of which 100 were type 2 diabetic patients and 100 were age and sex matched healthy non-diabetic controls. Mean serum magnesium level was significantly ($p < 0.001$) lower in type 2 diabetic patients when compared to that of non-diabetic healthy controls. Also, mean serum magnesium level is significantly lower in uncontrolled diabetic patients when compared to that of controlled diabetics.

KEY WORDS:

Type 2 Diabetes, Hypomagnesemia, serum magnesium

INTRODUCTION

Diabetes mellitus is a syndrome of impaired carbohydrate, protein and fat metabolism due to lack of secretion of insulin. Although diabetic patients have a normal lifestyle, its late complications will result in reduced life expectancy and major health cost. These include macrovascular diseases which leads to increase in prevalence of peripheral vascular disease, coronary artery disease, stroke and microvascular damage which leads to nephropathy, retinopathy and neuropathy.

Magnesium is present in higher concentration within the cell and it is the second most abundant cation next to potassium. It plays an important role in manipulating important biological pyrophosphate compounds. The disturbance in magnesium level i.e., hypomagnesemia has been reported to be occur in diabetic patients.

Although diabetes can induce hypomagnesemia, magnesium deficiency has also been proposed as a risk factor for diabetes. Animal studies have shown that magnesium deficiency has a negative effect on post receptor signalling of insulin. Some short term metabolic studies suggested that magnesium supplementation has a beneficial effect on insulin action and glucose metabolism.

Persistent hypomagnesemia leads to raised glucose level, insulin resistance and the degree of magnesium depletion positively correlates with serum glucose concentration and degree of glycosuria.

The cause of hypomagnesemia was attributed to (1).Osmotic renal loss from glycosuria, (2). Decreased intestinal absorption of magnesium. Recently a specific tubular magnesium defect in patients with diabetes has been postulated. Hypermagnesuria results specifically from reduction in tubular absorption of magnesium.

AIMS AND OBJECTIVES

1. To compare the level of serum magnesium in type 2 diabetes patients and non diabetic healthy controls.
2. To study the level of serum magnesium in controlled and uncontrolled diabetics.

REVIEW OF LITERATURE

MAGNESIUM:

Magnesium is the eighth most common element in earth's crust. Oceans and rivers are the most plentiful source of biologically available magnesium. Magnesium is easily dissolved in water and it is more soluble than calcium salts. Magnesium is the central ion of chlorophyll in plants. Magnesium is the fourth most abundant cation in vertebrate animals and it is the second most intracellular cation next to potassium¹. Magnesium salts are used traditionally as antacid and laxatives in the form of magnesium hydroxide, magnesium citrate, magnesium sulphate and magnesium chloride.

CHEMICAL CHARACTERISTICS:

Symbol: Mg

Element category: alkaline earth metal.

Atomic number: 12

Valency: 2

Crystal structure: hexagonal

Atomic radius: 0.65 angstrom unit

Atomic weight: 24.305 g/mol

Specific gravity: 1.738

No. of hydration cells: 2 layers

Melting point: 648.8 °C

Boiling point: 1090 °C

Magnesium cannot be passed through narrow channels in biological membranes unlike calcium because it cannot be easily stripped of its hydration shell. Proteins which transport magnesium have to recognize the large hydrated cation and strip of its hydration shell and deliver the dehydrated ion to transmembrane transport pathway through the membrane.

PHYSIOLOGICAL ROLE OF MAGNESIUM IN THE BODY:

Most animals contain approximately 0.4 g magnesium / kg. Human body contains around 20mmol/kg of magnesium in fat free tissue.

DISTRIBUTION:

Ninety nine percent of total body magnesium is present in muscles, bone and non muscular soft tissues². Fifty to sixty percent of magnesium resides as the hydroxyapatite mineral component of bone. As age

increases, magnesium content in bone decreases. During acute changes in serum magnesium concentration, bone provides a large exchangeable pool. One-third of skeletal magnesium is exchangeable and serves as the reservoir to maintain physiological extracellular magnesium. Intracellular magnesium concentrations range from 5 to 20mmol/L, of which 1 to 5 percent is in ionised form and the remainder is bound to proteins, adenosine triphosphate (ATP) and negatively charged molecules. Extracellular magnesium is about 1% of total body magnesium and it is found mainly in serum and red blood cells (RBCs).

Extra cellular magnesium exist in three fractions – ionised/free, protein bound and complexed with anions like phosphate, bicarbonate and sulphate or citrate³. Out of these three fractions, ionised magnesium has the greatest biological activity.

Magnesium acts as a cofactor in more than 300 enzyme regulated reactions, particularly reactions forming and using ATP. There is a direct effect on sodium (Na^+), potassium (K^+) and calcium (Ca^{2+}) channels. Magnesium acts as an essential cofactor for enzymes concerned with cell respiration and glycolysis. Activity of Sodium-Potassium ATP-ase depends on magnesium.

Magnesium can affect enzyme activity by binding in the active site and causing conformational changes during catalytic process and also by promoting aggregation of multi enzyme complexes. Magnesium also affects permeability characteristics and electrical properties of cell membrane. Reduced extracellular magnesium concentration increases membrane excitability in tissues.

Magnesium also acts to maintain a low resting concentration of intracellular calcium. Magnesium competes with calcium for membrane binding sites and stimulates calcium sequestration by sarcoplasmic reticulum. ATP metabolism, normal neurological function, muscle contraction and relaxation and release of neurotransmitters are magnesium dependent.

Magnesium also regulates vascular tone, bone formation and heart rhythm. Magnesium has a role in insulin secretion. Magnesium is considered as a natural 'calcium antagonist'. Magnesium inhibits calcium induced cell death and antagonizes calcium overload triggered apoptosis.

FUNCTIONS OF MAGNESIUM:

The various functions of magnesium are as follows:

1. ENZYME FUNCTION:

(A) Enzyme substrate:

Hexokinase

Protein kinase

Creatine kinase

Sodium potassium ATPase

Calcium ATPase

Adenylate cyclase

Guanylate cyclase

(B) DIRECT ENZYME ACTIVATION:

Phosphofructokinase

Creatine kinase

Adenylate cyclase

5-phosphoribosyl-pyrophosphate synthetase

Sodium potassium ATPase.

2. MEMBRANE FUNCTION:

Cell adhesion

Transmembrane electrolyte flux

3. CALCIUM ANTAGONIST:

Membrane contraction/relaxation

Neurotransmitter release

Action potential conduction in nodal tissue

4. STRUCTURAL FUNCTION:

Proteins

Nucleic acid

Polyribosomes

Mitochondria

Multiple enzyme complexes

REGULATION OF MAGNESIUM INFLUX AND EFFLUX:

Exchange of intracellular and extracellular magnesium in mammalian myocardium, fat tissue, renal parenchyma, brain tissue,

skeletal muscle and lymphocyte occurs in different rates. In man, equilibrium for magnesium is reached very slowly in most tissue compartments.

MAGNESIUM CONSUMPTION:

Humans have to consume magnesium regularly to prevent its deficiency. Recommendations in literature suggests lower daily minimum magnesium intake of 350mg for men, 280 to 300mg for women, 355mg during pregnancy and lactation.

SOURCES OF MAGNESIUM:

Magnesium is found abundant in nature. Magnesium content in food varies widely.

It is present in green leafy vegetables, chlorophyll, cocoa derivatives, nuts, wheat, seafood and meat.

Legumes, fish and fruits have intermediate magnesium concentration.

Dairy products have low magnesium concentrations.

All processed foods have low concentration of magnesium than unrefined food products.

RECOMMENDED DIETARY ALLOWANCE OF MAGNESIUM:

	Recommended dietary allowances(RDA)	
	Age	Magnesium(mg/day)
Infants	0-5 months	40
	5 months-1 year	60
Children	1-3 years	80
	4-6 years	120
	7-10 years	170
Males	11-14 years	270
	15-18 years	400
	19-22 years	350
	23-50 years	350
	Above 50 years	350
Females	11-14 years	280
	15-18 years	300
	19-22 years	280
	23-50 years	280
	Above 50 years	280
Pregnancy		320
Lactating women		355

MAGNESIUM ABSORPTION AND EXCRETION:

Magnesium homeostasis comprises three systems- kidney, bone and small intestine.

Magnesium is absorbed in the small intestine and gets stored in the bone and excess of it gets excreted in urine and faeces.

Kidneys mainly regulate serum magnesium. About 2400 mg of magnesium passes through kidneys daily of which 5 percent (120 mg) is excreted through urine. Major site of magnesium homeostasis in kidney is loop of Henle in which 65 percent of magnesium gets reabsorbed⁴.

Magnesium is mainly absorbed in the small intestine by a passive paracellular mechanism. A minor fraction of magnesium is transported through transcellular transporter TRPM (Transient Receptor Potential channel Melastatin member) 6 and TRPM 7. Around 24 to 76% of magnesium is absorbed from the gut and the rest is eliminated in the faeces. Intestinal absorption of magnesium does not depend on magnesium intake but it is dependent on magnesium status. When magnesium level is low, intestinal absorption of magnesium gets increased and vice versa.

LABORATORY ASSESSMENT OF MAGNESIUM:

Serum /Plasma Magnesium Concentration:

It provides an approximate guide to the presence or absence of magnesium deficiency⁵. Hypomagnesemia reliably indicates magnesium deficiency.

Magnesium concentration in muscle:

Muscle contains about 27% of total magnesium. Needle biopsy is used to find concentration of magnesium in muscle but it is an invasive procedure and it requires special skills.

Mononucleated white cell magnesium concentration:

It is the possible index for intracellular magnesium⁶. In humans, it does not correlate with erythrocyte or serum concentration. It is the better indicator for cardiac arrhythmia associated with magnesium deficiency.

Magnesium retention test (loading test):

Oral/ IV magnesium loading tests are described and it is used for diagnostic purpose. In normal individuals, all injected magnesium is excreted in urine within 24 to 48 hours after administration. If the retention of infused magnesium is less than 30%, it suggests magnesium deficiency unlikely. Precautions to be taken before performing this test -

patient should have normal kidneys, should not have taken any medication affecting magnesium excretion in kidney and should not have cardiac conduction disturbances.

METHODS USED TO MEASURE MAGNESIUM:

Serum magnesium is measured by various techniques like titration, precipitation, photometry, fluorometry and flame emission spectroscopy. In most of the techniques, precipitation of magnesium by 8-hydroxy quinolone is the basis for magnesium measurement. Now, enzymatic method is used with hexokinase or other enzymes that utilise Mg-ATP as the substrate⁷. Today most commonly used technique in many laboratories is photometric method⁸.

Photometric method:

A number of metallochromatic dyes / indicators are used and it changes colours by selectively binding with magnesium.

Calmagite – a metallochromatic indicator forms coloured complex when it binds with magnesium in alkaline solution and it is measured at 530 to 550 nm⁹. To prevent interference by calcium, specific calcium chelating agent EGTA [Ethylene Glycol- O,O- bis(2- aminoethyl) N,N Tetra Acetic acid] is added. To avoid the heavy metal complex formation

potassium cyanide (KCN) is added. Polyvinylpyrrolidone and surfactant are also included to reduce the interference from lipemia and protein¹⁰.

Methylthymol blue – forms blue complex when binds with magnesium and it is measured at 600nm. To prevent interference by calcium, EGTA is added.

Magon or xylidyl blue binds with magnesium in alkaline medium and forms red complex¹¹. Protein and calcium interference is prevented respectively by dimethyl sulfoxide and EGTA respectively¹².

Specimen:

Serum is the preferred specimen. Anticoagulants like oxalate, EDTA and citrate should not be used because they form complexes by binding with magnesium. When serum is kept at 4°C, magnesium is stable for days and when frozen, it is stable for months. Serum/plasma should be separated from red blood cells or clot as early as possible to avoid false increase in magnesium levels due to cell leakage.

Reference value:

Reference interval for serum magnesium is 0.70 to 0.99 mmol/L (1.3 to 2.5 mEq/L).

CLINICAL SIGNIFICANCE:

HYPERMAGNESEMIA:

Under normal physiological conditions, magnesium is excreted in urine. Hypermagnesemia occurs when renal function is impaired or when there is excess of magnesium load.

Causes¹³:

1. Renal failure
2. Magnesium infusion
3. Primary hyperparathyroidism
4. Diabetic ketoacidosis
5. Adrenal insufficiency
6. Tumour lysis syndrome
7. Milk alkali syndrome

Clinical features:

Symptoms are ranging from asymptomatic to life threatening events.

Magnesium concentration of 4 to 6 mEq/L leads to nausea, lethargy, headache and sluggish deep tendon reflexes.

Magnesium concentration of 6 to 10 mEq/L leads to hypocalcemia, somnolence, absent reflex and hypotension.

Magnesium concentration more than 10 mEq/L leads to complete heart block, muscle paralysis, respiratory and cardiac arrest.

Management:

It can be prevented by avoiding magnesium load in patients with impaired renal function tests. Stopping magnesium supplements with normal renal function will allow restoration of magnesium to normal levels. I.V Calcium gluconate can be used as magnesium antagonist. In severe life threatening hypermagnesemia and in patients with renal failure hemodialysis is indicated.

HYPOMAGNESEMIA:

Hypomagnesemia is common in ICU settings with nutrition, diuretics, etc. In the presence of hypomagnesemia, renal excretion of magnesium is decreased. Hypomagnesemia also occurs in gastrointestinal and renal losses. It is often associated with hypokalemia, hypocalcemia and metabolic acidosis.

Causes:

1. Chronic diarrhoea
2. Steatorrhoea
3. Malabsorption syndrome
4. Small bowel resection
5. Alcoholics
6. Acute pancreatitis
7. Diuretics – both loop and thiazides
8. Bartter and Gitelman syndrome
9. Primary aldosteronism
10. Hypercalcemia
11. Drugs- Aminoglycosides, proton pump inhibitors, cisplatin
12. Hungry bone syndrome following parathyroidectomy
13. Transplant kidney
14. Diabetes mellitus
15. Pregnancy
16. Respiratory alkalosis

Clinical features:

Neuromuscular – Weakness

Tremor

Muscle fasciculation

Dysphagia

Positive chvostek's sign

Positive trousseau's sign

Cardiac –

Arrhythmias

Hypertension

Tachycardia

CNS –

Depression

Agitation

Psychosis

Nystagmus

Seizures

Metabolic – Hypokalemia

Hypocalcemia

ECG changes – Widening of QRS complex

Flattening of T waves

QTc prolongation

ST segment depression

Prolonged PR interval

Ventricular arrhythmia

Management:

Correct the underlying cause of hypomagnesemia. Replacement of magnesium by oral route in asymptomatic patients and those with mild deficiency by supplementing sustained release formulations. I.V magnesium is required in patients with tetany and ventricular arrhythmia.

MAGNESIUM DEFICIENCY IN DIABETES:

Magnesium ion has an important fundamental role in metabolism of carbohydrate and particularly in the action of insulin¹⁴. Magnesium acts as a cofactor of various enzymes involved in carbohydrate oxidation.

Magnesium is involved in multiple steps in insulin secretion, insulin binding and activity. It is a cofactor for adenylate cyclase and ATPase. Recently it has been proposed that magnesium plays a novel factor in pathogenesis of complications in diabetes. Relation between magnesium and carbohydrate intolerance, insulin resistance, accelerated atherosclerosis, hypertension, dyslipidemia has been observed.

It is important to recognize the symptoms and signs of diabetes associated magnesium deficiency because its deficiency occurs long before its reflection in serum values. It has been suggested that there is prevalence of 25 to 39% of magnesium deficiency associated with diabetes mellitus.

Hypomagnesemia in diabetes indicates secondary magnesium deficiency. Mechanism for magnesium deficiency in diabetes mellitus is not exactly known. It has been proposed that osmotic diuresis is responsible for magnesium loss. Glycosuria, which accompanies the diabetic state, impairs the magnesium reabsorption from renal tubules. Magnesium is principally reabsorbed in proximal tubule (30%), ascending loop of Henle (65%) with minimal (1 to 5%) reabsorption in distal convoluted tubule. Glucose is a crucial part in maintaining cellular ion homeostasis, increasing intracellular calcium level and decreasing intracellular magnesium level. Influence of magnesium on ATPase

activity in cell membrane and consequently on sodium, potassium and calcium metabolism play a role in diabetic complications. Sodium potassium ATPase which is necessary to maintain intracellular potassium is a magnesium dependent enzyme. Impaired enzymatic activity plays a role in pathogenesis of diabetic polyneuropathy.

Possible causes of hypomagnesemia in diabetes:

1. Reduced renal reabsorption
2. Enhanced filtered load
3. Enhanced gastrointestinal loss
4. Decreased intake

MAGNESIUM DEFICIENCY AND OXIDATIVE STRESS:

Diabetes is a state of increased free radical activity¹⁵. It is associated with increased prevalence of atherosclerotic disease and cardiovascular morbidity and mortality. Lipid peroxidation is a consequence of free radical activity which plays an important role in atherosclerosis, aging and late diabetic complications. Glutathione, which is thiol containing tripeptide, is present in plasma in reduced state. It has antioxidant properties. Magnesium acts as a cofactor for enzymatic reaction of glutathione synthesis.

MAGNESIUM DEFICIENCY AND CARDIOVASCULAR DISEASE:

Magnesium has some relationship with pathogenesis of atherosclerosis and hypertension and diabetes. Several studies have shown that there is magnesium deficiency in hypertensive animals and there is inverse relationship between diastolic blood pressure and intracellular magnesium ion¹⁶. Some studies have shown that at the onset of pathogenesis there is alteration in ionic metabolism in which there is increase in intracellular calcium and decrease in intracellular magnesium.

The pathophysiological disorders due to magnesium deficiency in cardiovascular system are vasospasm, free radical generation, increase in vasoconstrictor activity, increase in intracellular calcium in smooth muscle and cardiac muscle, formation of pro-inflammatory agents. These contribute to blood pressure modification during magnesium deficiency. Magnesium depletion directly cause vasoconstriction and hypertension and predispose to cardiac arrhythmias and sudden death. Magnesium deficiency is also associated with hyperlipidemia¹⁷.

Thus Magnesium deficiency in diabetes gains importance as it increases the complications of diabetes and other associated systemic illnesses.

DIABETES MELLITUS:

Diabetes mellitus is a metabolic disorder of multiple etiology, characterised by chronic hyperglycemia with disturbances of carbohydrate, protein and fat metabolism resulting from defects of insulin secretion, insulin action or both. Sustained exposure to these abnormalities is accompanied by microvascular complications (retinopathy, nephropathy and neuropathy) as well as macrovascular complications (stroke, myocardial infarction and peripheral arterial vascular disease).

PHYSIOLOGICAL ANATOMY OF PANCREAS:

It is composed of two major tissues – acini and islets of Langerhans. Acini secrete digestive juices into the duodenum. Islets of Langerhans secrete insulin and glucagon directly into the blood.

Human pancreas contains 1 to 2 million islets, each islet is about 0.3 mm in diameter. It is organised around the blood vessels (small capillaries) so that it secrete hormones directly into the blood.

There are three major cell types present in islets

- Alpha cell
- Beta cell
- Delta cell

Each cell is distinguished from one another by their staining and morphological characteristics.

Nearly 60% of islets are made up of beta cells. It lies in middle of the islet. It secretes mainly two hormones – insulin and amylin. Amylin secretes in parallel with insulin secretion and its role is unclear.

Nearly 25% of islets contain alpha cells. It secretes glucagon.

Nearly 10% of islets contain delta cells. It secretes somatostatin.

There is another type of cell which is present in small number – PP cell, which secretes pancreatic polypeptide.

There is close interrelationship exists between these cell types

- Amylin inhibits insulin secretion
- Insulin inhibits glucagon secretion
- Somatostatin inhibits both insulin and glucagon secretion.

INSULIN AND ITS METABOLIC EFFECTS:

Insulin secretion is associated with energy abundance. When food contains excess carbohydrate, it stimulates insulin secretion in large amount. In turn, it plays important role in storing these excess energy in

the form of glycogen in liver and muscles and by converting to fats and gets deposited in adipose tissue¹⁸. It also promotes aminoacid uptake by the cells.

INSULIN CHEMISTRY:

Aminoacid chain: 2 (each connected by disulfide linkage)

Molecular weight: 5808

When these 2 aminoacid chains are split, it loses its functional activity.

SYNTHESIS OF INSULIN:

First it begins with insulin RNA translation that occurs in ribosomes attached to ER(Endoplasmic Reticulum). It forms 'insulin prohormone' (molecular weight: 11,500). Then it is cleaved in ER to form 'proinsulin'. Proinsulin has no insulin activity. Then cleavage occurs in golgi apparatus to form insulin and peptide fragments.

When insulin is secreted into the blood stream, it is mostly in unbound form. So it is rapidly cleared from the blood within 10 mins. It is degraded by the 'insulinase enzyme' which is secreted from the liver. So its plasma half life is about 6 minutes.

INSULIN RECEPTOR:

It is an enzyme linked receptor. It contains four subunits- 2 alpha and 2 beta units which are linked by disulfide bond.

2 alpha subunits- lie entirely outside the cell membrane

2 beta subunits- penetrate through membrane and protrudes into cytoplasm. Autophosphorylation occurs in beta subunits and activate tyrosine kinase.

EFFECTS OF INSULIN STIMULATION:

1. Within seconds, it increases the uptake of glucose within the muscle cell and adipose tissue by increasing glucose transport by increase in translocation of intracellular vesicles to the cell membrane.
2. It makes cell membrane more permeable to transport potassium ions, amino acid and phosphate ions.
3. Within minutes, it changes the activity of many intracellular metabolic enzymes.
4. Much slower effect occurs in hours/days - formation of new proteins by changing the rates of translation of mRNA (messenger RNA) at ribosomes.

EFFECT OF INSULIN ON METABOLISM OF CARBOHYDRATE:

Most of the day, muscle depends mainly on fat for its energy source and not glucose. Muscle cell resting membrane is less permeable to glucose. When insulin concentration increases, it makes cell membrane more permeable to glucose¹⁸. Conditions in which the muscle utilises glucose are (a) after moderate/heavy exercise (b) few hours after the meal.

If the muscle is not exercising after the meal, yet large amount of glucose is transported into muscle cells – then this excess glucose is converted into glycogen and stored.

One of the most important effects of insulin is the storage of glycogen in liver. Mechanisms by which insulin cause uptake and storage of glucose in liver includes

- It inactivates liver phosphorylase thereby preventing breakdown of glycogen.
- It activates glucokinase enzyme thereby increasing uptake of glucose into liver cells and it gets phosphorylated.
- It promotes glycogen synthase enzyme and it helps in monosaccharide unit polymerisation to form glycogen.

Thus, the liver removes excess glucose from the blood after the meals and once the blood glucose falls in between the meals, the stored glucose is released back into the blood.

Insulin promotes conversion of excess glucose in the liver into fatty acids and it is subsequently stored as triglycerides in VLDL (Very Low Density Lipoprotein).

Insulin also decreases the activity and quantity of liver enzymes that is required for gluconeogenesis and inhibits it.

EFFECTS OF INSULIN IN FAT METABOLISM:

Effects of insulin in long term in fat metabolism are equally important. Long term effect of lack of insulin causes atherosclerosis, stroke, MI and other vascular disorders.

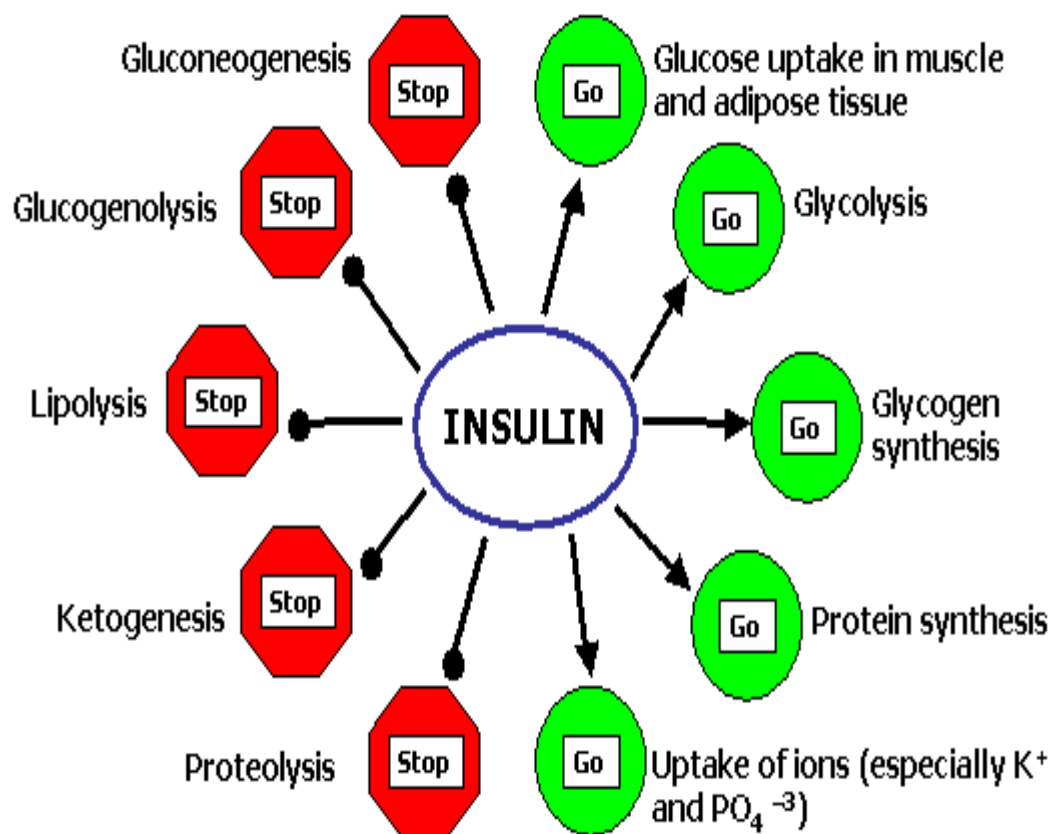
Factors that lead to increased fatty acid synthesis and storage are

- Once the glycogen concentration reaches 5 to 6% in the liver, glycogen synthesis gets stopped. Then this excess glucose is converted to fatty acid by activating glycolytic pathway. In glycolytic pathway, pyruvate is produced. It is converted into acetyl CoA (acetyl coenzyme A), that acts as a substrate for fatty acid synthesis.

- In Krebs cycle (citric acid cycle), glucose is converted into citrate and isocitrate, thereby activating acetyl CoA carboxylase, fatty acids are synthesised.
- Insulin activates lipoprotein lipase enzyme in the capillary wall of adipose tissue. There triglycerides are broken down into FFA (free fatty acid) and gets absorbed into adipose tissue. Within adipose tissue these FFA are again converted back to triglycerides and stored.
- Insulin inhibits hormone-sensitive lipase action, thereby preventing breakdown of triglycerides in the adipose tissue.

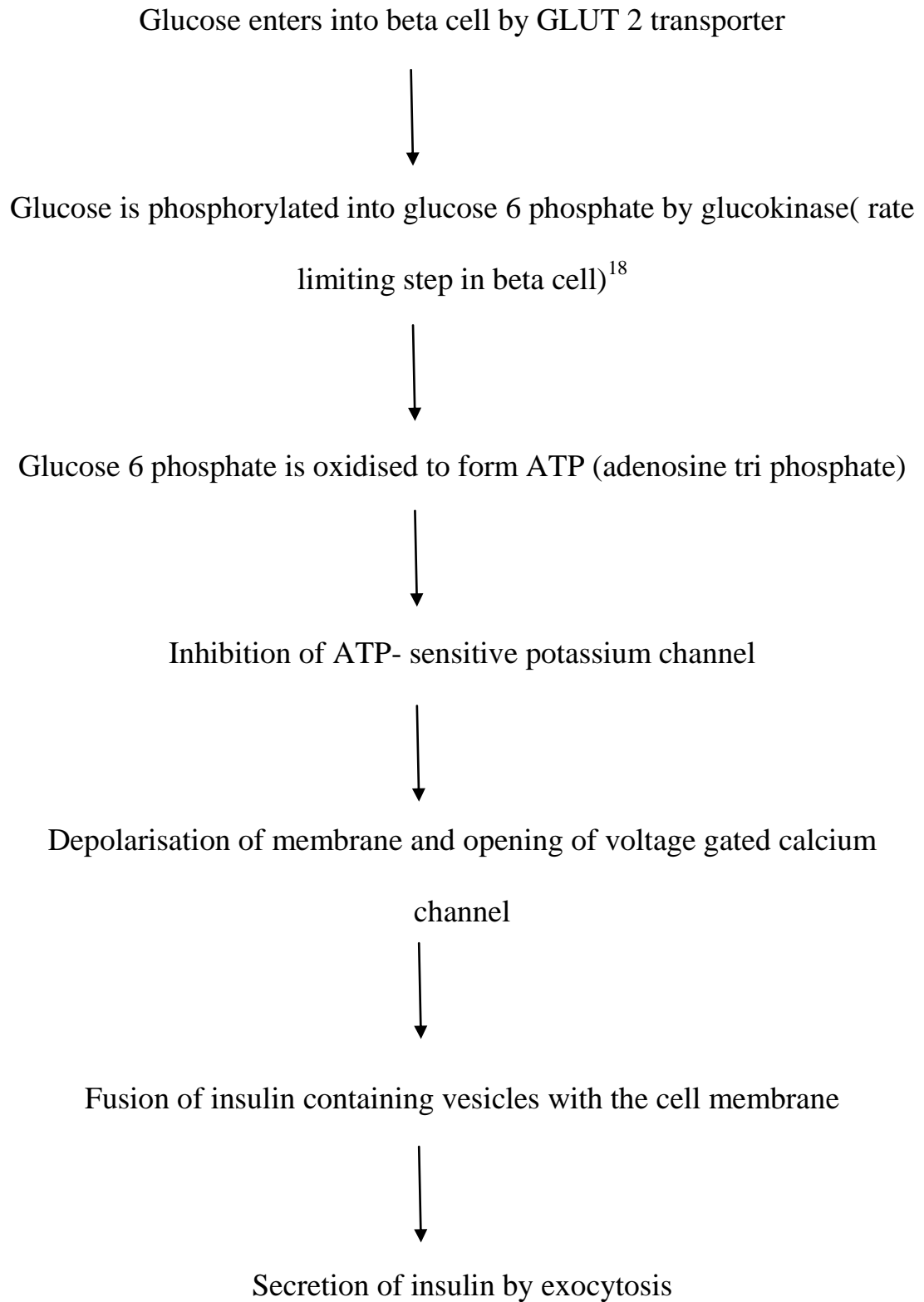
EFFECTS OF INSULIN IN PROTEIN METABOLISM AND GROWTH:

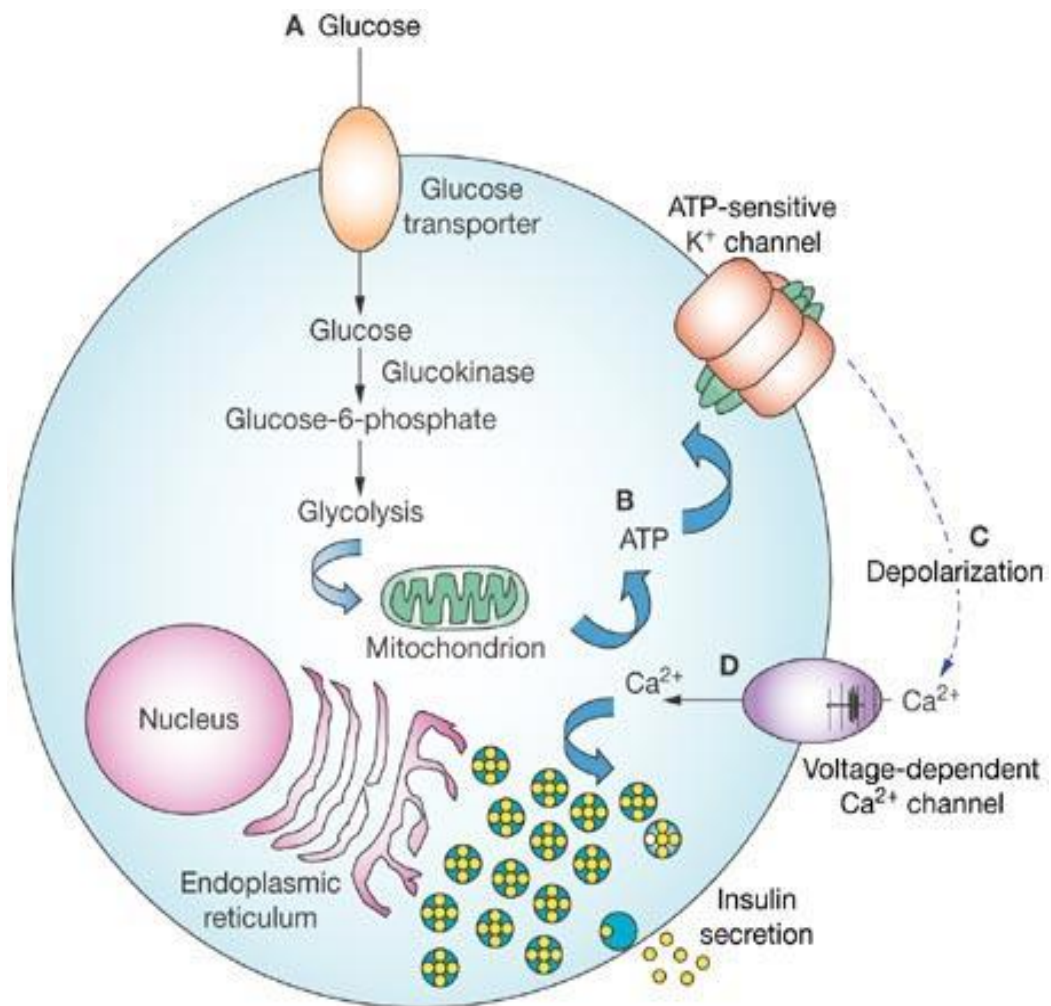
- Insulin stimulates the uptake of many amino acids like valine, leucine, isoleucine, tyrosine and phenylalanine.
- Insulin acts as 'on and off' mechanism in ribosomes. It helps in formation of protein by translation of mRNA.
- It inhibits protein catabolism, thereby preventing release of amino acid from the cell.
- Insulin and growth hormone act synergistically to promote growth.



This diagram represents the actions of insulin.

MECHANISM OF INSULIN SECRETION:





This picture represents the secretion of insulin in response to glucose stimulation.

FACTORS MODULATING INSULIN SECRETION:

There are various gut hormones which modulate the secretion of insulin. They are GLP-1(glucagon like peptide), GIP 1 and 2 (glucose dependent insulintropic peptide), cholecystokinin , secretin , vasoactive intestinal polypeptide, and gastrin.

FACTORS THAT INCREASE INSULIN SECRETION:

- Increased blood glucose
- Increased free fatty acid in blood
- Increased amino acid in blood
- Glucagon, growth hormone
- Cortisol
- Acetyl choline
- Parasympathetic stimulation
- Insulin resistance
- Obesity
- Gastrointestinal hormones like gastrin, secretin
- Sulfonylurea drugs
- Beta adrenergic stimulation

FACTORS THAT DECREASE INSULIN SECRETION:

- Decreased blood glucose
- Somatostatin
- Alpha adrenergic activity
- Leptins
- Fasting

CONTROL OF INSULIN SECRETION:

Rate of insulin secretion rises rapidly when the blood glucose concentration increases above 100mg/100ml of blood.

When blood glucose concentration reaches 400 to 600 mg/100ml, insulin secretion reaches a peak of 10 to 25 times the basal level.

When the blood glucose comes back to fasting level, insulin secretion gets turn off within 3 to 5 minutes. This response of insulin to an elevated blood glucose level provides an extremely important feedback mechanism for regulating blood glucose concentration.

ETIOLOGICAL CLASSIFICATION OF DIABETES MELLITUS:

In 1997, ADA Expert committee on the Diagnosis and Classification of diabetes mellitus recommended modifications in the

classification system which was developed by National Diabetes Data Group (NDDG) and Diabetes mellitus is classified on the basis of pathogenesis,(as opposed to earlier criteria such as age of onset or type of therapy), into two broad categories as type 1 and type 2¹⁹ .

It also includes eight other specific types of diabetes.

1. Genetic defects of beta cell function
2. Genetic function in insulin action
3. Diseases of exocrine pancreas
4. Endocrinopathies
5. Drug/chemical induced
6. Infections
7. Uncommon forms of immune mediated diabetes
8. Other genetic syndromes associated with diabetes

TYPE 1 DIABETES:

Type 1 diabetes mellitus is the result of complete or near total insulin deficiency due to cell-mediated autoimmune pancreatic β -cell destruction and they are prone to develop ketoacidosis.

Aetiology is unknown. It may be immune mediated or idiopathic. This is usually diagnosed in children and young adults but may be diagnosed in adults also. Markers of this process include

autoantibodies to insulin, islet cell autoantibodies and antibodies to glutamic acid decarboxylase.

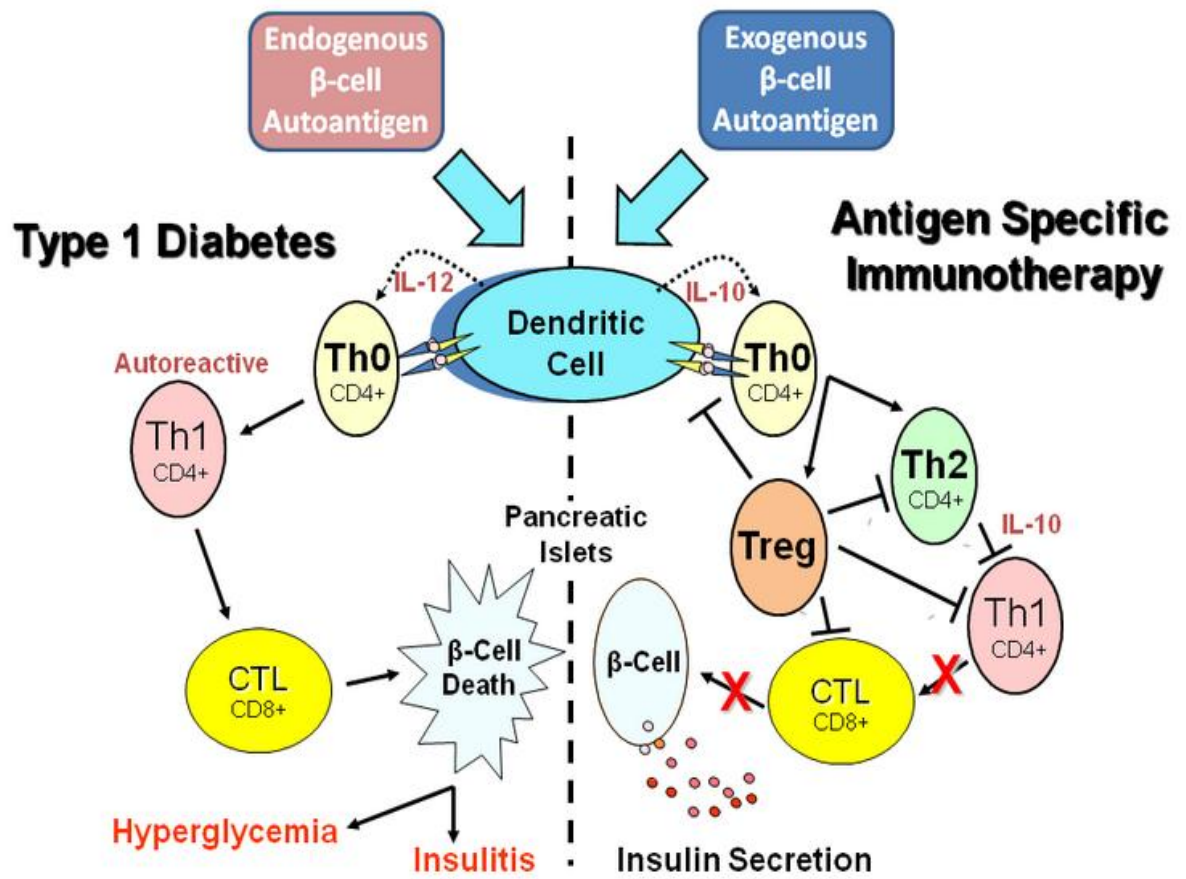
At the time of diagnosis of type 1 diabetes, one or more autoantibodies are present in around 90% cases.

It is associated with other autoimmune conditions like vitiligo, addisons disease, pernicious anemia, grave's disease and Hashimoto's thyroiditis.

Type 1 diabetes has strong HLA associations which can either be protective or predisposing. IDDM 1 gene encoded within HLA region remains the most important powerful determinant of type 1 diabetes which accounts for approximately 40% of familial inheritance.

Some patients have permanent insulinopenia and they develop diabetic ketoacidosis without any evidence of autoimmunity. It is termed as idiopathic diabetes. It is not HLA associated and lacks immunological evidence.

Individuals with this form of diabetes may have episodic ketoacidosis and exhibits varying degree of insulin deficiency in between the episodes.



This figure illustrates the pathophysiology of type 1 diabetes.

TYPE 2 DIABETES:

Type 2 diabetes mellitus is a heterogenous group of disorders characterised by varying degrees of insulin resistance, impaired insulin secretion and increased glucose production. This is the most common form and remains asymptomatic for years. It is commonly seen in adults but can occur in childhood. Although insulin level in these patients appears normal/elevated, its level is always low when it is compared with elevated plasma glucose level. It has strong genetic predisposition.

Risk of the disease increases with age, physical inactivity and obesity. It occurs more frequently in individuals with hypertension, dyslipidemia and in women with prior gestational diabetes.

EPIDEMIOLOGY:

According to International Diabetes Federation, 285 million adults were estimated to have diabetes in 2010. Prevalence may soar to 438 million in 2030 if proper prevention and control measures are not undertaken. Increase in prevalence is attributed to increasing obesity due to physical inactivity and the aging of the population. Type 2 diabetes constitutes majority (80 to 95 percent) of adult onset diabetes and its incidence is increasing in childhood and juvenile onset disease. Around 70 percent of people with diabetes live in developing countries (China

and Indian subcontinent). The variability in the incidence of both type 1 and type 2 diabetes mellitus is likely due to genetic, behavioural and environmental factors. According to Indian council of Medical Research, the prevalence of diabetes in India in 2000 was 12 to 19 % in urban and 4 to 9 % in rural areas.

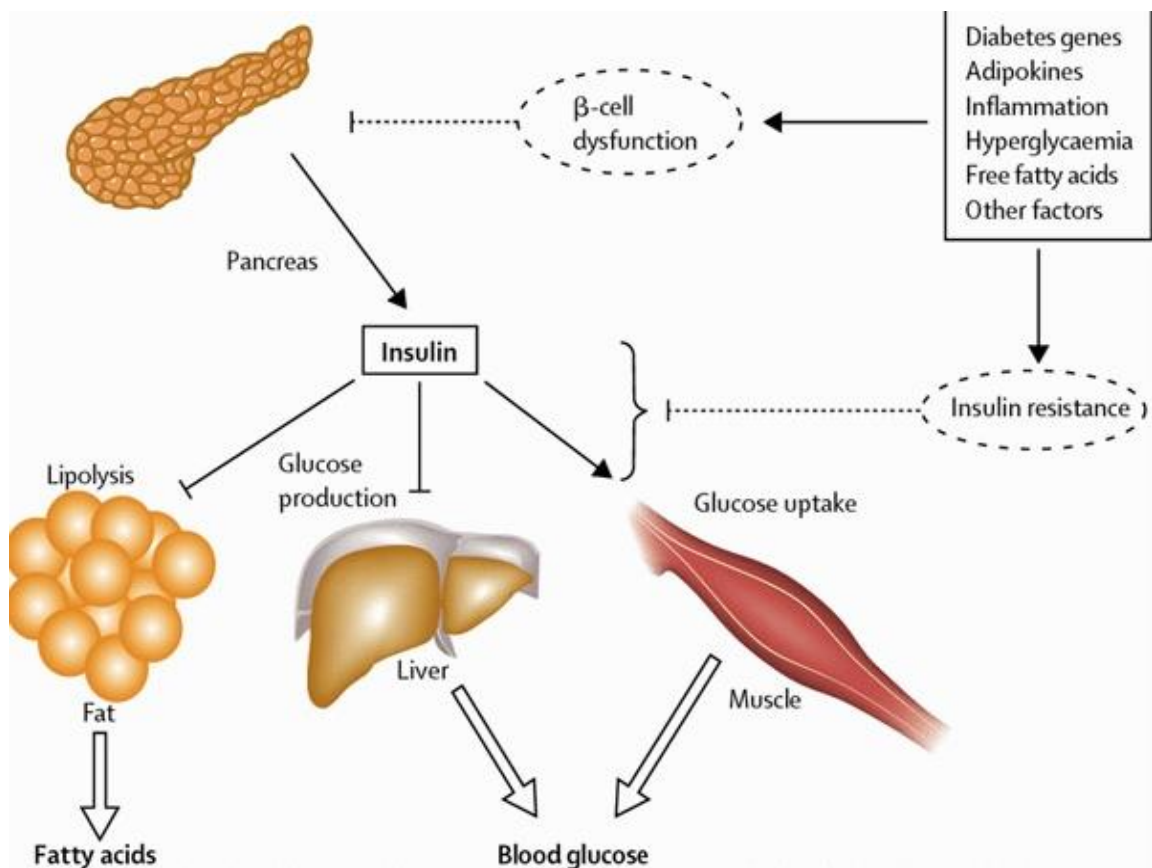
AGE OF ONSET:

The age of onset of type 2 diabetes mellitus is 4th to 5th decade of life however the age of onset has been dropping steadily over the years, especially in ethnic groups of high prevalence. In Asia, the characteristics of diabetes are different from western countries with lower age of onset, low BMI, greater visceral adiposity and a reduced insulin secretory capacity. There is no sex predilection.

RISK FACTORS FOR TYPE 2 DIABETES MELLITUS:

- Positive family history
- Race/ethnicity (pacific islands , African American, Asians)
- Physical inactivity
- Obesity($\text{BMI} \geq 25 \text{ kg/m}^2$)
- History of GDM or delivery of baby >4 kg

- Hypertension
- H/o cardiovascular disease
- HDL <35 mg/ dl and/or triglycerides > 250 mg/dl
- Polycystic ovary syndrome or acanthosis nigricans²⁰



This diagram illustrates the effects of insulin in various organs

GENETIC CONSIDERATIONS OF TYPE 2 DIABETES MELLITUS:

Type 2 diabetes mellitus is a disorder with a strong genetic component. The concordance in identical twins is 70 to 90 percent. The risk of developing disease in an individual approaches to 40 percent if both parents are diabetic. Genetically type 2 diabetes mellitus has both monogenic and polygenic forms.

Now 36 genetic loci has been identified which contributes to risk of type 2 diabetes. Incidence is high among Latinos/Hispanics, aboriginal people in America and Australia, Indian and Pacific ocean island populations and people of Indian subcontinent²¹.

The genes predisposing to type 2 diabetes mellitus are not completely identified. For now, around 20 candidate genes are screened for association with type 2 diabetes mellitus of which calpain-10, peroxisome proliferator activated receptor-gamma, transcription factor 7-like 2 gene , Kir 6.2 and hepatocyte nuclear factor-4 α are important. Many of them predispose to obesity which in turn lead to diabetes. These susceptibility genes are likely to cause the disease by altering islet function or insulin secretion. In non-obese Asian Indians ENPP-1 K121Q is one of the susceptibility genes and it causes insulin resistance.

MONOGENIC FORMS OF TYPE 2 DIABETES MELLITUS:

The genetic etiology is clear in this form of type 2 diabetes mellitus. They show an autosomal dominant inheritance.

- Phenotype characterised by defective insulin secretion
 - Maturity onset diabetes of the young (MODY)
 - Mutations in the insulin or proinsulin genes
 - Mitochondrial gene mutations
- Phenotype characterised by insulin resistance
 - Lipoatrophic diabetes
 - Mutations in insulin receptor gene
 - Type A insulin resistance
 - Leprechaunism
 - Rabson- Mendenhall syndrome
 - Mutations in the PPAR- gamma gene

ENVIRONMENTAL FACTORS:

- Increased caloric consumption
- Medications

- Stress
- Decreased exercise

The disease is caused by the interaction of adverse environmental factors with genetic factors i.e., altering the expression of genes.

INSULIN RESISTANCE:

It is defined as ‘decrease in the activity of endogenous or exogenously administered insulin to alter the metabolism in target tissues’²². Most of the individuals will maintain normal glucose level by increasing insulin production by beta cells to compensate for decrease in action of insulin. In susceptible individuals, there is failure of beta cells to maintain high level of insulin secretion or increasing in insulin resistance which results in progressive glucose intolerance and subsequent development of diabetes. Genetic factors play a role in both in propensity to develop insulin resistance and beta cell failure in response to insulin resistance.

Sites of insulin resistance:

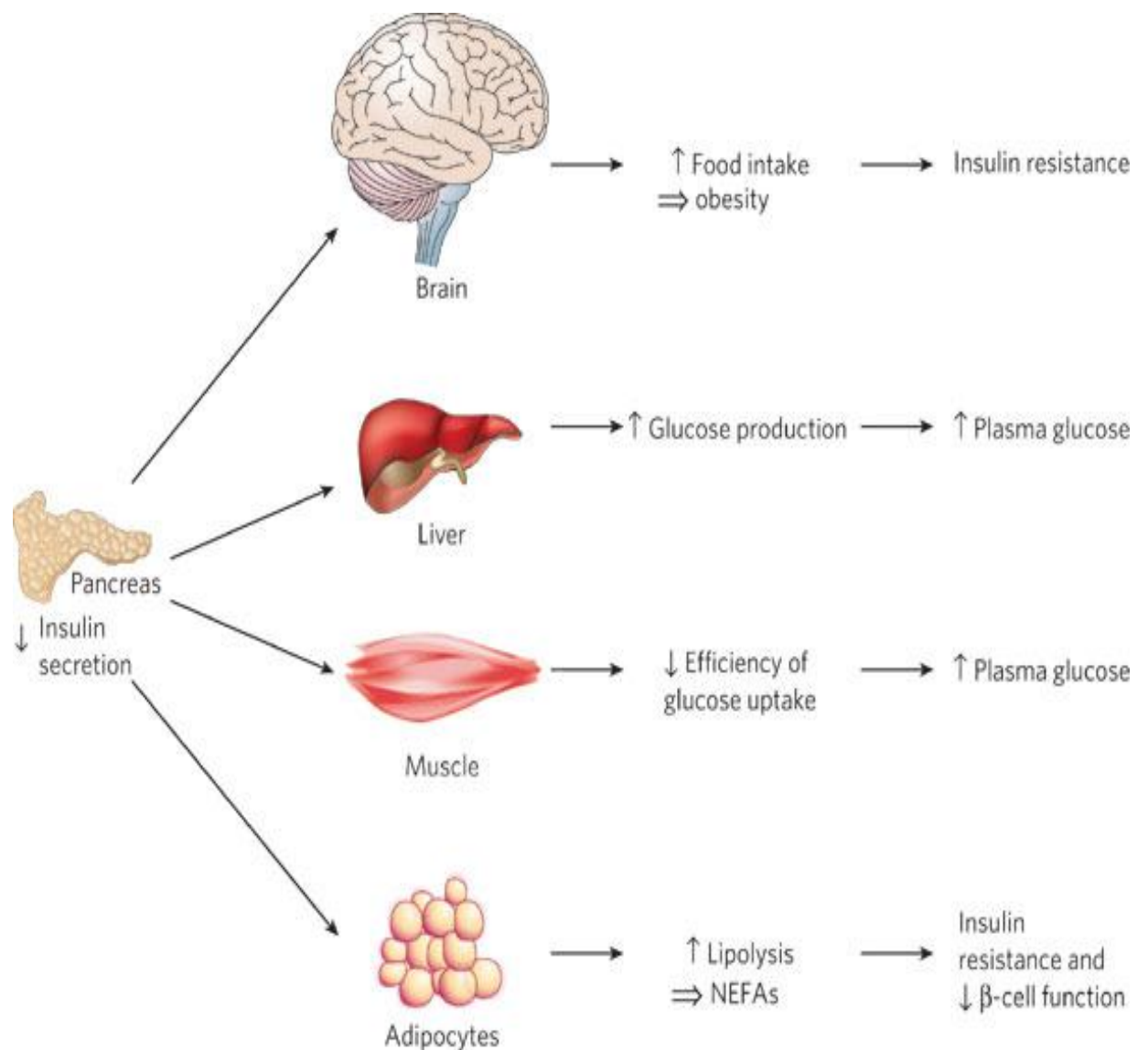
- Skeletal muscle
- Adipose tissue
- Liver

Mechanism of insulin resistance:

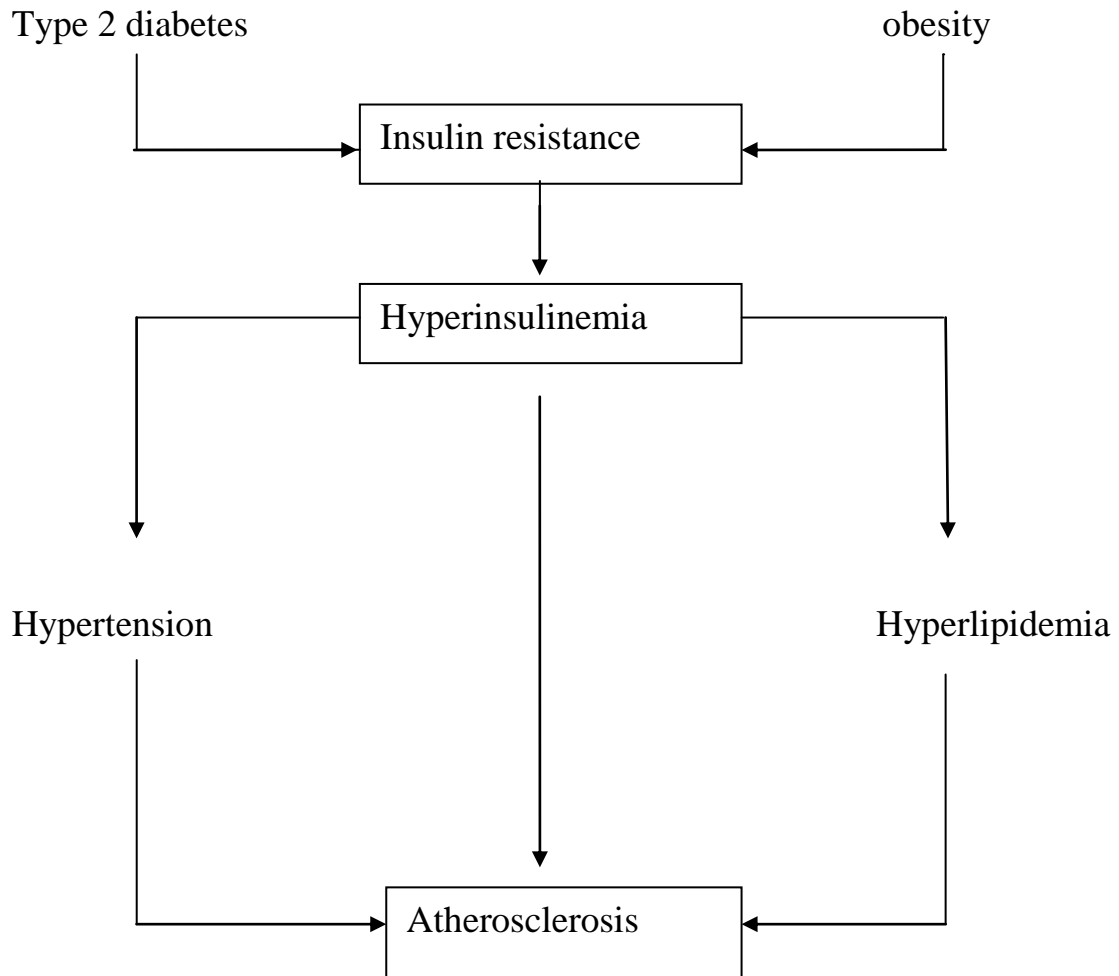
Alteration in tyrosine kinase phosphorylation , altered post receptor events and other signal regulatory proteins are responsible for the resistance. It is also due to abnormal insulin or insulin receptor. Sustained hyperglycemia can cause failure to enhance hexosamine pathway that leads to glucotoxicity resulting in increased glucosamine level. Increased glucosamine produce insulin resistance in both skeletal muscle and adipose tissue. Sustained hyperinsulinemia produce insulin resistance by down regulation of insulin receptor. Main site of insulin resistance occurs in post receptor level.

The beta subunit in insulin receptor undergoes serine-threonine phosphorylation besides tyrosine autophosphorylation. It is responsible for increasing insulin resistance and therefore it impairs signal transduction. In insulin resistance state, the GLUT-4 is not depleted, but its translocation is hampered.

Type 2 diabetes is often associated with other conditions like obesity, hyperlipidemia and hypertension.



This figure illustrates the pathophysiology of type 2 diabetes & insulin resistance



DEFECTS IN INSULIN SECRETION:

Insulin sensitivity is an important factor in determining the magnitude of insulin response to beta cell stimulation by glucose. Pattern of insulin release is abnormal. First phase of insulin release is absent or blunted, whereas second phase is enhanced and prolonged, resulting in hyperinsulinemia. 50% of beta cell function is already lost at the time of diagnosis. In islets, free fatty acid (FFA) is required for insulin

production. However excess FFA result in reduction of glucose stimulated insulin release.

INITIAL EVALUATION OF PATIENT WITH DIABETES:

Medical history:

- Age of onset of disease
- Family history
- Eating patterns and nutritional status
- Growth and development in children and adulthood
- Diabetes education history
- Previous treatment regimens and its response
- Current treatment (including medication, physical activity, meal plan)
- History of diabetes related complications
 - Microvascular: nephropathy, retinopathy, neuropathy (sensory, including history of foot lesion; autonomic, including sexual dysfunction and gastroparesis)
 - Hypoglycaemia awareness
 - Any severe hypoglycaemia : frequency and cause
 - Macrovascular: CAD, CVA, peripheral arterial disease
 - Others: psychosocial problems, dental disease

- Other endocrine disorders

Physical examination:

- Height , weight, BMI
- Blood pressure (including orthostatic measurement)
- Fundus examination
- Thyroid palpation
- Skin examination (for insulin injection site & acanthosis nigricans)
- Complete foot examination:
 - Inspection
 - Palpation of dorsalis pedis and posterior tibial artery
 - Presence/absence of patellar and ankle reflex
 - Determination of proprioception, vibration and 10g monofilament test.

Lab evaluation:

- Fasting lipid profile
- Liver function test
- Spot PCR
- Serum creatinine and eGFR
- HbA1c
- Thyroid function test

Referrals:

- Annual dilated eye exam
- Family planning for women of reproductive age
- Registered dietitian for medical nutritional therapy
- Diabetes self management education
- Dental examination
- Mental health professional(if needed)

GESTATIONAL DIABETES:

It is glucose intolerance developing during pregnancy. About 50% of women with GDM (Gestational Diabetes Mellitus) develop type2 diabetes in their later life. So, screening for gestational diabetes is recommended in all pregnant women, who are not known to have diabetes, between 24th and 28th week of pregnancy.

A 75-g OGTT is done in the morning after overnight fasting for at least 8 hours with plasma glucose monitoring at fasting, 1 hour and 2 hours. Diagnosis of gestational diabetes is made if any of the values are exceeded.

- Fasting : ≥ 92 mg/ dl (5.1 mmol/ L)
- 1 hour : ≥ 180 mg/ dl (10.0 mmol/L)
- 2 hour: ≥ 153 mg /dl (8.5 mmol/L)

Screening For Gestational Diabetes:

Risk assessment at 1st prenatal visit:

- Marked obesity
- Previous GDM
- Glycosuria
- Features suggestive of diabetes

If testing is negative, re-testing should be done at 24 to 28 weeks of gestation.

During initial prenatal visit, if high risk women is found to have diabetes by using standard criteria for diabetes, they should receive a diagnosis of 'overt' diabetes, not gestational diabetes.

EFFECTS OF MATERNAL HYPERGLYCEMIA ON FOETUS:

In first trimester:

- Growth retardation
- Foetal wastage
- Malformations

In second trimester:

- Foetal loss

- Pre-eclampsia
- Polyhydramnios
- Hypertrophic cardiomyopathy
- Placental insufficiency

In third trimester:

- Respiratory distress syndrome
- Macrosomia
- Hyperbilirubinemia
- Hypomagnesemia
- Hypocalcemia
- Intrauterine death

DIAGNOSIS OF DIABETES MELLITUS:

Criteria for screening ²³:

- Fasting plasma glucose ≥ 100 mg/dl
- Random plasma glucose ≥ 130 mg/dl
- HbA1c $> 6.0\%$
 - If screening test is negative, again screening should be done in 3 years
 - If screening test is positive, but the result is below diagnostic threshold- do another test using different method for diagnosis

- If screening test is positive and the result is above the diagnostic threshold but the second test does not reach the threshold, again do test in one year.

Criteria for diagnosis:

- Fasting plasma glucose ≥ 126 mg/dl
- Random plasma glucose ≥ 200 mg/dl
- 2 hour OGTT ≥ 200 mg/dl
- HbA1c $\geq 6.5\%$
 - Diagnosis requires confirmation, unless equivocal symptoms of hyperglycemia are present.

Interpretation of HbA1c:

Normal : $< 5.7\%$

Pre-diabetes: 5.7 % to 6.4 %

Diabetes : 6.5% or more

COMPLICATION OF DIABETES:

ACUTE:

1. **Hypoglycemia:** occurs in patients treated with insulin or insulin secretagogues. It is due to disturbance in balance between food

intake and appropriate drug dosage. Exercise, alcohol intake and decreased liver/kidney function precipitate this imbalance.

2. **Hyperosmolar hyperglycemic nonketotic syndrome**²⁴-

characterised by

- (a) severe hyperglycemia(blood glucose > 600mg/dl)
- (b) absence of significant ketosis
- (c) serum hyperosmolality (>340mOsm/kg)
- (d) profound dehydration

Typically the patient develops altered sensorium, excessive thirst and signs of severe dehydration.

Precipitating causes are

- Infection
- Diabetic gangrene
- UTI
- Septicaemia
- Extensive burns
- Myocardial infarction
- Pancreatitis
- Alcoholism
- Peritoneal and hemodialysis

- Surgical stress
- Drugs like steroids, immunosuppressive agents.

Dehydration, electrolyte abnormalities, hyperglycemia and hyperosmolar condition should be corrected with appropriate fluids, insulin and potassium.

3. **Diabetic ketoacidosis-**

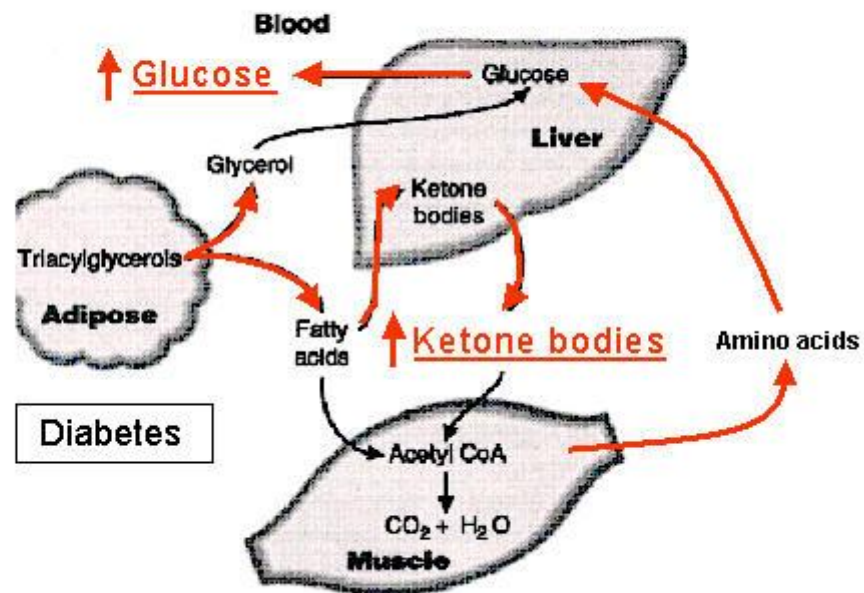
Characterised by

- (a) Hyperglycemia
- (b) Hyperketonemia
- (c) Metabolic acidosis

4. **Infection** – common infections in diabetes are tuberculosis, malignant otitis externa, pyelonephritis, pneumonia, staphylococcal infection, periodontal infection, candidiasis, mucormycosis, hepatitis C, HIV infection.

5. **Lactic acidosis-** when lactic acid level is more than 5 mmol/L in the blood.

Energy metabolism, untreated diabetes



This diagram represents the formation of ketone bodies in untreated diabetes

CHRONIC:

MACROVASCULAR COMPLICATION:

- CAD (Coronary Artery Disease)
- PAD (Peripheral Arterial Disease)
- CVA (Cerebro Vascular Accident)

About 75 to 80 percent of all diabetic patients will die prematurely due to cardiovascular disease (CVD), particularly CHD (Coronary Heart Disease).

❖ **Cardiovascular disease:**

Adults with diabetes have heart disease death rates about 2 to 4 times more than that of adults without diabetes. Type 2 diabetes patients have 3 to 6 fold increase in rate of myocardial infarction. Common co-existing conditions like obesity, hypertension, dyslipidemia (decrease HDL, increase triglycerides, altered LDL particle size and number), hypercoagulability are also cardiovascular risk factors.

❖ **Cerebrovascular disease:**

TIA (Transient Ischemic Attack) and stroke are more common in diabetics than non-diabetics. Haemorrhagic stroke is less common. Prognosis is worse in diabetic patients. Recurrent stroke and stroke related dementia are frequent in diabetics.

❖ **Peripheral arterial disease:**

It is 2 to 3 times more common in diabetic males and 5 to 6 times more common in diabetic females. Clinical feature include intermittent claudication pain, critical limb ischemia and gangrene.

MICROVASCULAR COMPLICATIONS:

❖ Diabetic Retinopathy:

The risk of developing retinopathy depends upon duration of diabetes and degree of hyperglycemia. It starts from hyperglycemia induced vascular injury. Histological lesion is thickening of basement membrane in retinal capillaries and loss of pericytes. It is classified as proliferative and non-proliferative diabetic retinopathy. Most of the patients are asymptomatic in initial stages. Since the onset and duration of disease is unknown in type 2 diabetes, fundus examination should be done at the time of diagnosis. Most common cause of vision loss in these patients is due to development of macular edema.

The ETDRS study (Early Treatment of Diabetic Retinopathy Study) defined CSME (Clinically Significant Macular Edema) as follows²⁵:

- Retinal thickening at/within 500 μ m from the centre of macula
- Hard exudates at/within 500 μ m from the centre of macula (if associated with thickening of adjacent retina)
- Zones of retinal thickening at least 1 disc area in size, part of which is within 1 disc diameter of the centre.

All patients with diabetes (both type 1 and type 2) are at risk of developing retinopathy. Early detection and appropriate management can reduce the risk of visual loss in these patients.

❖ **Diabetic neuropathy:**

Classification:

- **Symmetrical polyneuropathies:**
 - Large fibre neuropathy
 - Small fibre neuropathy
 - Autonomic neuropathy
 - Distal sensory polyneuropathy
- **Asymmetrical neuropathies:**
 - Cranial neuropathy
 - Truncal neuropathy
 - Lumbosacral radiculopathy
 - Limb mononeuropathy
 - Entrapment neuropathy
- **Combinations:**
 - Polyradiculo neuropathy
 - Diabetic neuropathic cachexia
 - Symmetrical polyneuropathies

According to the American Academy of Neurology, diabetic neuropathy is diagnosed in the presence of autonomic or somatic neuropathy when other causes causing neuropathy are excluded. At least two out of five criteria are needed to diagnose: symptoms, signs, electro-diagnostic testing, quantitative autonomic and sensory testing. Bed side examinations include sensation of pin prick, assessment of muscle pain, touch, temperature, vibration and tendon reflexes. Compound action potential amplitude is initially normal, as the disease progresses it declines. Treatment is aimed to prevent progression of neuropathy and to provide symptomatic relief. Based on the evidence that it has an autoimmune basis, immunosuppressive therapies like immunoglobulin, corticosteroids and plasma exchange has been tried in lumbosacral radiculoneuropathy.

❖ **Diabetic nephropathy:**

It is characterised by excessive albumin excretion in urine due to loss of kidney function. The hallmark of diabetic nephropathy is proteinuria. Mechanism of proteinuria – Increased filtration, increased tubular secretion and decreased tubular absorption. It is the leading cause for ESRD (End Stage Renal Disease). Most of the diabetic patients suffering from advanced renal disease require renal replacement therapy.

❖ **Diabetic foot:**

Classical triad:

- Neuropathy
- Ischemia
- Infection

Wagner's classification:

Grade 0: No ulcer in high risk foot

Grade 1: Superficial ulcer

Grade 2: Deep ulcer penetrating upto tendon/bone/joint

Grade 3: Deep abscess/osteomyelitis

Grade 4: Localised gangrene

Grade 5: Extensive gangrene that requires amputation

Warning symptoms of diabetic foot:

▪ **Vascular:**

- Cold feet
- Intermittent claudication
- Pain at rest, especially nocturnal

- **Neurologic:**

- Burning/tingling sensation
- Pain and hypersensitivity
- Cold feet
- Weakness
- Diminished sweating

- **Musculoskeletal:**

- Gradual change in foot shape
- Sudden painless change in foot shape without history of trauma.

- **Dermatological:**

- Painless wounds
- Slow healing/ non healing wounds
- Chronic scaling, itching
- Recurrent infection(paronychia, athlete's foot)

FACTORS CONTRIBUTING TO FOOT ULCER:

Extrinsic factors:

- Inappropriate foot wear
- Object inside the shoes
- Walking bare foot

- Sharp injuries
- Falls and accidents

Intrinsic factors:

- Joint deformity
- Callus
- Limited joint motility
- Bony prominences
- Fissures
- Previous foot surgery

CHARCOT FOOT:

Charcot joint is defined as relatively painless progressive arthropathy of single/ multiple joints. Most common site is tarsal-metatarsal region. Other sites are metatarsophalangeal joint, ankle and subtalar joint. Usually, minor trauma is the precipitating event.

Prevention of diabetic foot includes:

- Primary prevention – screening of high risk foot and advice on preventive footwear
- Secondary prevention – management of foot lesion

- Tertiary prevention – prompt referral to specialist for advanced foot lesion.

METABOLIC SYNDROME:

Type 2 diabetes and glucose intolerance are also the manifestations in metabolic syndrome²⁶.

Diagnosis of metabolic syndrome:

ATP III criteria: (three or more of the following)

1. Abdominal obesity- waist circumference >102cm(male) and >88cm(female)
2. Hypertriglyceridemia ≥ 150 mg/dl
3. Low HDL : < 40mg/dl(male) and <50mg/dl(female)
4. High BP: $\geq 130/85$ mm Hg
5. High fasting glucose : ≥ 110 mg/dl

WHO criteria:

1. High blood pressure : $\geq 160/90$ mm Hg
2. Hyperlipidemia : TGL > 150mg/dl ., HDL < 35 mg/dl
3. Central obesity: waist to hip ratio > 0.90 (men) and >0.85(women)
or BMI > 30 kg/m²
4. Microalbuminuria: urine albumin excretion rate ≥ 20 µg/min

MANAGEMENT:

Major management goals are

- ❖ To prevent both micro and macrovascular complications.
- ❖ To avoid symptoms due to drug adverse effects, hyperglycemia and its complications.

Specific goals of therapy:

- ❖ Elimination of symptoms
- ❖ Optimizing glycemic parameters
- ❖ Achieve and maintaining a ideal body weight
- ❖ Maintaining blood pressure control
- ❖ Maintain optimal lipid profile
- ❖ Achieve optimal health and well-being

Recommended treatment modalities:

- ❖ Diet modification
- ❖ Exercise
- ❖ Pharmacological intervention

Recommended targets for adults with diabetes:

- Glycemic control : A1c <7
- Preprandial plasma glucose : 70 to 130 mg/dl
- Postprandial plasma glucose: <180mg/dl
- Blood pressure: <130/80mmHg
- LDL cholesterol : <100mg/dl
- HDL cholesterol : >40mg/dl
- Triglycerides : <150mg/dl

Medical nutritional therapy:

Since obesity is the major risk factor, nutritional therapy is the cornerstone in treating type 2 diabetes²⁷. A registered dietitian expertise in diabetes is the team member to deliver Medical Nutritional Therapy (MNT)

It involves

- Assessment : evaluation of individual life style and his food intake
- Goal setting: goals to be set in which areas that person needs improvement

- Intervention : by nutritional plans, life style change and exercise
- Evaluation
- Monitoring progress and measure outcome indicators

Goals of MNT:

- To achieve normal range in glucose level
- To achieve normal lipid profile
- To achieve ideal range of BP
- Improving the quality of life

Nutritional intervention and recommendations:

- Modest weight loss (5 to 7%) shown to improve insulin resistance
- Physical activity and behaviour modification helpful in maintenance of lost weight
- Effective meal plan
- Weight loss medications in obese and overweight persons (combined with life style changes)
- Bariatric surgery when BMI > 35kg/m²
- Five non nutritive sweeteners approved by FDA (saccharin, aspartame, acesulfame K , neotame, sucralose)

- Protein intake of 15% to 20% of total energy intake is sufficient.
- Limit saturated fat to less than 7%
- Minimise the intake of trans fatty acid

Exercise:

Benefits of increased physical activity:

- Improves insulin sensitivity and glucose tolerance
- Weight loss and maintenance of ideal body weight
- Improved cardiovascular risk factors
- Enhanced work capacity
- Reduction in insulin dosage or need for insulin/drugs
- Improving the sense of well-being and quality of life

Medical evaluation should be done before prescribing exercise and it includes

- Determination of glycemic control
- CVS examination(BP, peripheral pulse, bruit)
- Neurological examination
- Dilated fundus examination especially if proliferative diabetic retinopathy is suspected/present

Precautions for patients with complications:

- Insensitive feet / peripheral vascular insufficiency
 - Avoid running
 - Choose cycling, walking or swimming
 - Proper foot wear and daily foot examination should be emphasised
- Untreated/ recently treated proliferative retinopathy

Avoid exercise associated with

- Valsalva maneuvers
 - Rapid head movements
 - Increased intra-abdominal pressure
- Hypertension
 - Avoid valsalva maneuvers
 - Avoid heavy lifting

The patient should start exercise slowly and then at regular intervals at least three to four times a week and then gradually increase the intensity, duration and frequency of exercise.

Aerobic exercise (biking, swimming, dancing, jogging) should be encouraged. In persons who are confined to chair, armchair exercise can be performed.

To improve glycemic control, at least 75 min/ week of vigorous aerobic exercise or 150 min/ week of moderate intensity aerobic exercise are recommended. Physical activity should be recommended for at least 3 days/week and not more than 2 consecutive days without physical activity.

Exercise increase the sensitivity of insulin in skeletal muscle and increases the glucose uptake. In high risk persons, regular exercise may delay/ prevent the progression of diabetes.

Pharmacological intervention:

Pharmacological intervention is an adjunct to but not as a substitute for exercise and dietary modification. At the time of diagnosis, metformin therapy should be started concurrently along with life style intervention.

The choice of antidiabetic agents is individualized according to patient's preference, contraindications/ comorbidities, social support and finances.

ORAL ANTIDIABETIC AGENTS:

It differs from one another in physiological effect, mechanism of action, pharmacokinetics and metabolism.

- **Insulin secretagogues** (sulfonylureas, repaglinide and nateglinide) stimulate insulin secretion from beta cells.
- **Biguanides** (metformin) reduces hepatic overproduction of glucose.
- **Alpha glucosidase inhibitors** inhibit the absorption of carbohydrate from intestine.
- **Thiazolidinediones** primarily work in fat and muscle and enhance insulin action.
- **Amylinomimetics** increase the activity of amylin with effects on weight and glucose.
- **Incretin mimetics** increase GLP-1 (Glucagon like peptide) activity with effects on glucose and weight.
- **DPP-4** (DiPeptidyl Peptidase IV) **inhibitors** increase the level of incretin hormones.
- In most of the patients, combination of these drugs is required to achieve target glycemic control.

SULFONYLUREAS:

Mechanism of action: It binds with SUR (sulfonyl urea receptor) which is present in ATP dependent potassium channel.

It is the drug of choice when life style intervention and metformin fails to achieve target glycemic control. Good responders include: (A) FBS < 200mg/dl, (B) preserved beta cell mass, (C) short duration of diabetes, (D) normal weight subject.

It is contraindicated in pregnancy, type 1 diabetes, severe infections and allergy to sulpha drugs.

Adverse effects are weight gain, hypoglycaemia, and hypersensitive reaction.

NON-SULFONYLUREA SECRETAGOGUES:

Mechanism of action is almost similar to that of sulfonylureas but the difference is that in binding site. It binds in SUR 1 subunit in ATP dependent potassium channel.

It is contraindicated in liver and renal disease.

Adverse effects are weight gain and hypoglycaemia (less common than sulfonylureas).

BIGUANIDES:

Metformin decreases hepatic glucose production by inhibiting hepatic gluconeogenesis and glycogenolysis. It increases the GLUT 4 (insulin sensitive) translocation to the cell membrane.

According to ADA guidelines, metformin is to be given in all type 2 diabetic patients in the absence of contraindications.

It is contraindicated in hepatic dysfunction, serum creatinine >1.5mg/dl, metabolic acidosis, alcohol abuse and congestive heart failure.

It should be withheld 24 hours prior to surgery and any radiological procedures that require contrast agents.

Adverse effects are dysgeusia, nausea, vomiting, lactic acidosis and vitamin B12 deficiency.

THIAZOLIDINEDIONES:

It is found to be a ligand for PPAR- γ (Peroxisome Proliferator Activated Receptor Gamma). Main action : Increase in adipogenesis and increase in insulin sensitive mediated glucose uptake in muscle. It is more useful in patients with insulin resistance.

It is contraindicated in liver disease and congestive heart failure.

Adverse effects are weight gain, oedema, anaemia, decrease bone mineral density and precipitation of heart failure.

ALPHA-GLUCOSIDASE INHIBITORS:

It is a competitive suppressant of alpha glucosidase, an enzyme that hydrolyses polysaccharides to monosaccharides, which is present in small intestine brush border. It can be used in combination with other drugs.

It is contraindicated in gastroparesis, inflammatory bowel disease and serum creatinine > 2mg/dl.

Adverse effects are diarrhoea, flatulence, abdominal discomfort and distension.

INSULIN PREPARATIONS:

CONVENTIONAL INSULIN:

1. Short acting insulin – regular insulin(human)

- Onset of action : 30 mins to 1 hour
- Peak in 2 to 3 hours
- Duration of action is 6 to 8 hours.

2. Intermediate acting insulin- NPH (Neutral Protamine Hagedorn)

- Onset of action: 1.5 hours
- Peak in 4 to 10 hours
- Duration of action is 16 to 24 hours

INSULIN ANALOGUES:

1. Rapid acting insulin:

- **Insulin lispro**

- Proline- lysine conversion in beta chain
- Onset of action : 0.2 to 0.5 hours
- Peak in 0.5 to 2 hours
- Duration of action is 3 to 4 hours

- **Insulin aspart**

- Aspartic acid for proline substitution in beta chain
- Onset of action: 0.2 to 0.5 hours
- Peak in 0.5 to 2 hours
- Duration of action is 3 to 5 hours

- **Insulin glulisine**

- Lysine for asparagine substitution in beta chain
- Onset of action : 0.2 to 0.5 hours
- Peak in 1 hour

- Duration of action is 4 hours

2. Long acting insulin:

- **Insulin glargine**

- Prolonged beta chain and glycine for asparagine substitution in alpha chain
- pH: 4
- Onset of action : 2 to 4 hours
- Duration of action : 20 to 30 hours
- Not approved for pregnant patients and children < 6 years of age

- **Insulin detemir**

- Acylation of lysine with saturated fatty acid in beta chain
- Onset of action : 1 to 2 hours
- Duration of action : 20 hours

INDICATION OF INSULIN THERAPY IN TYPE 2 DIABETES:

- FBS > 250mg/dl
- HbA1C > 10%
- Patients with osmotic symptoms/ketosis
- During inter-current illness

- Patient undergoing surgery
- During pregnancy

ADVERSE EFFECT OF INSULIN THERAPY:

- Hypoglycaemia (common)
- Weight gain
- Lipoatrophy (rare)
- Lipohypertrophy (rare)
- Insulin allergy (rare)

ASSESSMENT OF TREATMENT EFFICACY:

It should be monitored through a schedule of patient interviews and examinations with comprehensive assessment of:

- Continued patient acceptance of treatment plans and goals
- Symptoms
- Weight
- Blood pressure
- Smoking
- Screening evaluations include
 - Lipid levels
 - Urine microalbumin to creatinine ratio
 - Dilated eye exams

- Comprehensive foot examination
- Various parameters of glycemic control.

Patient can determine the effects of glycemic therapy by SMBG (Self Monitoring of Blood Glucose). They can use a daily journal to record food intake, exercise, doses of insulin/oral hypoglycaemic agent, symptoms and results of SMBG.

Multiple therapeutic agent and problem solving using SMBG results should make it possible for most patients to achieve glycemic control goals.

MATERIALS AND METHODS

STUDY POPULATION:

This study was conducted in 100 diabetic patients and 100 non- diabetic healthy controls who attended General Medicine OPD at Government Rajaji Hospital, Madurai.

Inclusion criteria:

1. Age 30 to 70 years
2. Positive History of diabetes

Exclusion criteria:

1. Hypertension
2. Gastrointestinal disorders
3. Impaired renal function
4. Alcoholic pancreatitis
5. Therapy with diuretics, aminoglycosides
6. Endocrine disorders
7. Heart disease
8. Not willing to give consent

DATA COLLECTION:

A detailed history with detailed clinical examination was done.

LABORATORY INVESTIGATIONS:

1. Fasting blood glucose
2. Postprandial blood glucose
3. Serum magnesium
4. HbA1c
5. Serum urea and creatinine
6. Urine analysis
7. ECG

STUDY PROTOCOL:

100 diabetic patients and 100 non diabetic healthy controls in the age group of 31 to 70 years attending General Medicine OPD were included. Blood samples were taken from each of the study groups and magnesium levels are assessed and compared between the case and control groups.

Blood pressure was recorded. Cardiovascular disease was ruled out by history and ECG. Urine was examined for proteinuria. FBS values

were assessed after 8 hours of fasting. PPBS values, Blood urea and serum creatinine values were measured.

Serum magnesium was determined by using photometric method. Calmagite – a metallochromatic indicator when binds with magnesium in alkaline medium, it forms red colour complex and it is measured at 530 to 550 nm. To prevent interference by calcium, specific calcium chelating agent EGTA is added. To avoid the heavy metal complex formation, KCN is added. Polyvinylpyrrolidone and surfactant are also included to reduce the interference from lipemia and protein. Intensity of colour formed is directly proportion to the amount of magnesium present in the sample.

DESIGN OF STUDY:

Case control study

PERIOD OF STUDY:

6 months (April 2014 to September 2014)

COLLABORATING DEPARTMENTS:

Department of Medicine

Department of Biochemistry

ETHICAL CLEARANCE:

The study was approved by the Institutional Ethical Committee.

CONSENT: Individual written and informed consent.

CONFLICT OF INTEREST: NIL

FINANCIAL SUPPORT: NIL

ANALYSIS: STATISTICAL ANALYSIS

The data collected was tabulated in a master chart. Statistical analysis was done by using Epidemiological Information Package (EPI 2010) developed by Centre for Disease Control, Atlanta, SPSS 20 and Sigma Stat 3.5 version. The association between means of continuous variables was assessed by using one way ANOVA test and independent student's t test and that of categorical variables with chi square test. A p value of less than 0.05 was taken as significant.

PARTICIPANTS:

100 diabetic patients and 100 age and sex matched non- diabetic controls attended General Medicine OPD at Government Rajaji Hospital, Madurai.

RESULTS

Table 1: AGE DISTRIBUTION

Age in years	Cases		Controls	
	Number	Percentage	Number	Percentage
31 - 40	14	14.0	15	15.0
41 - 50	42	42.0	40	40.0
51 - 60	24	24.0	26	26.0
61 - 70	20	20.0	19	19.0
Total	100	100.0	100	100.0
Mean \pm SD	50.39 \pm 9.76		50.01 \pm 10.15	

The mean age of cases and controls were 50.39 \pm 9.76 and 50.01 \pm 10.15 years respectively. The maximum number of patients was in the age group of 41-50.

Figure 1: AGE DISTRIBUTION

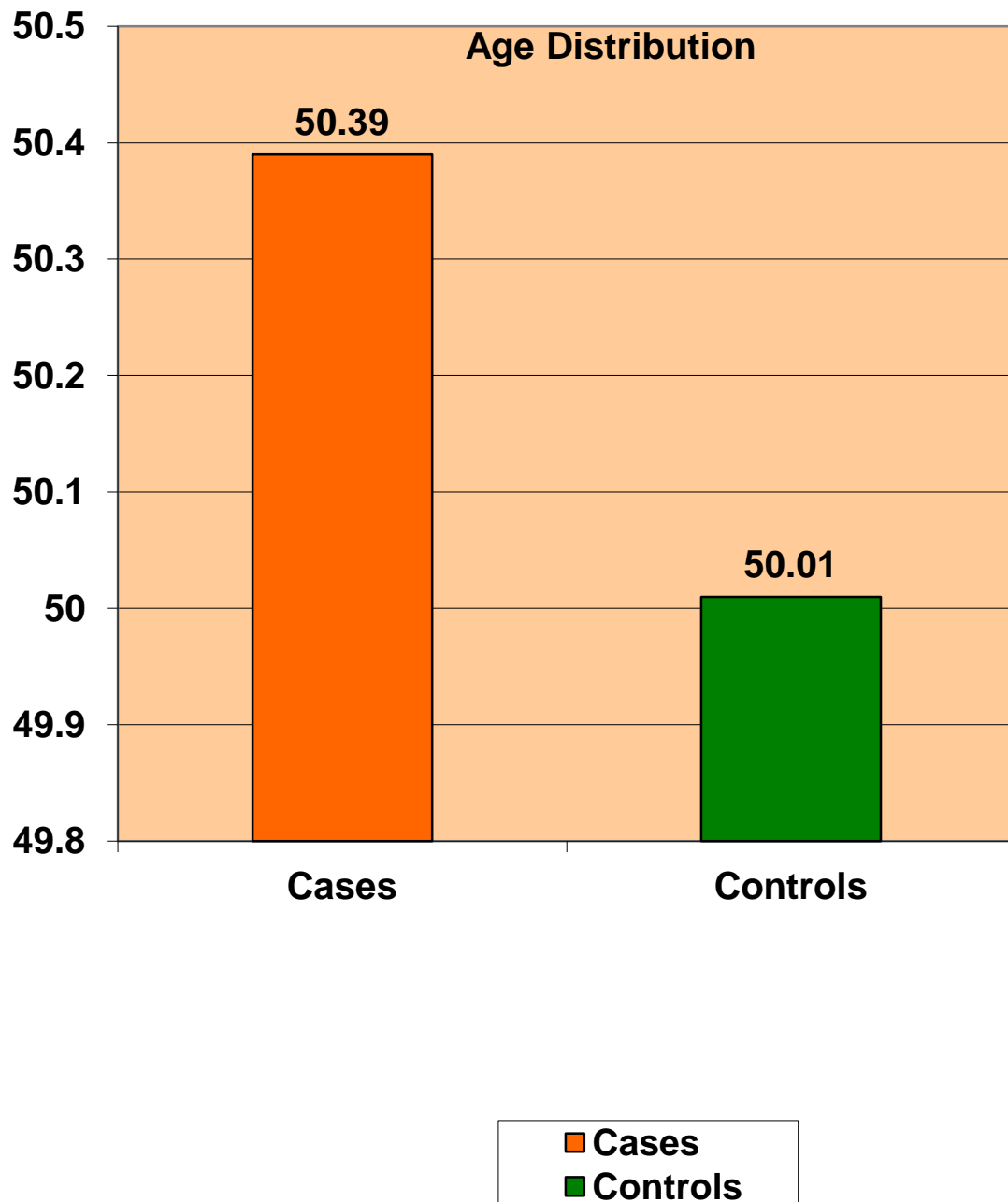


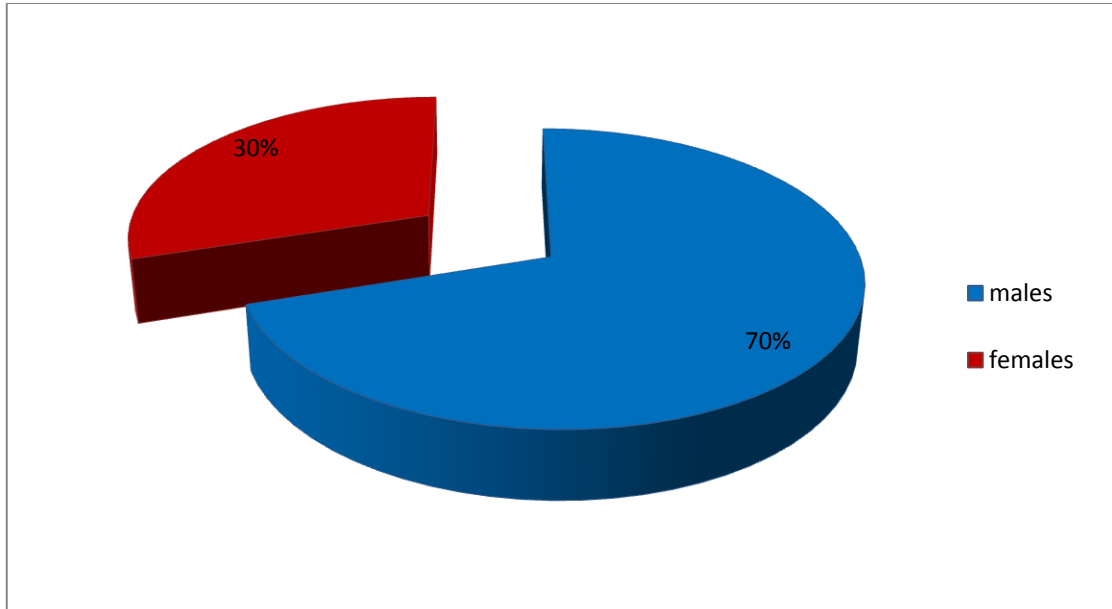
Table 2: SEX DISTRIBUTION

Sex	Cases		Controls	
	Number	Percentage	Number	Percentage
Male	70	70.0	70	70.0
Female	30	30.0	30	30.0
Total	100	100.0	100	100.0

Both among the cases and controls, the sex distribution were same i.e., 70% males and 30% females.

Figure 2: SEX DISTRIBUTION

Cases:



Controls:

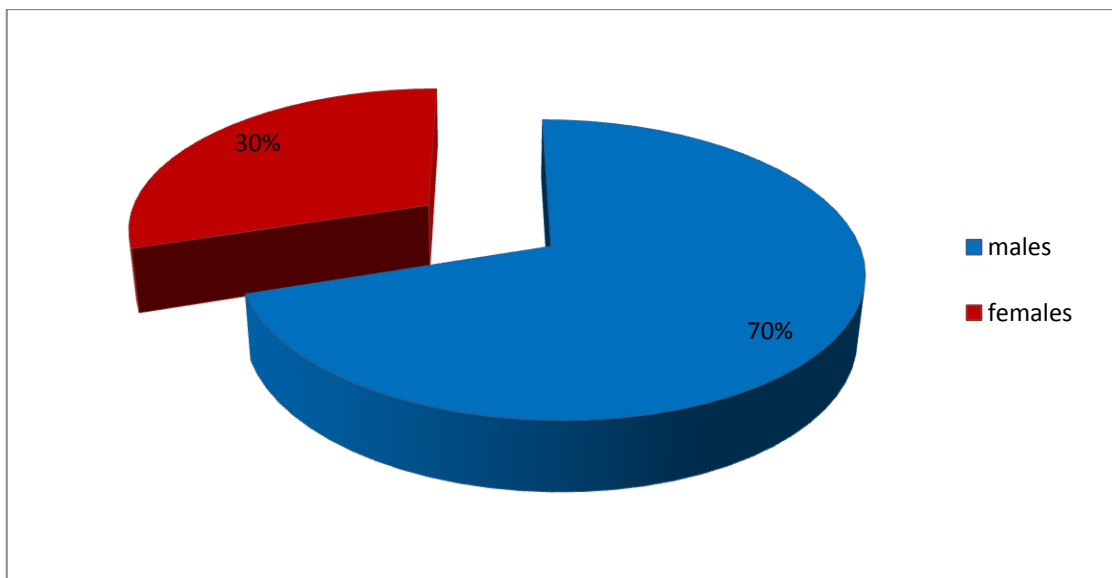


Table 3: MEAN PATTERN OF FBS

FBS(mg/dl)	Mean	SD	'p' value
Cases	102.42	11.16	<0.001
Controls	91.93	4.32	

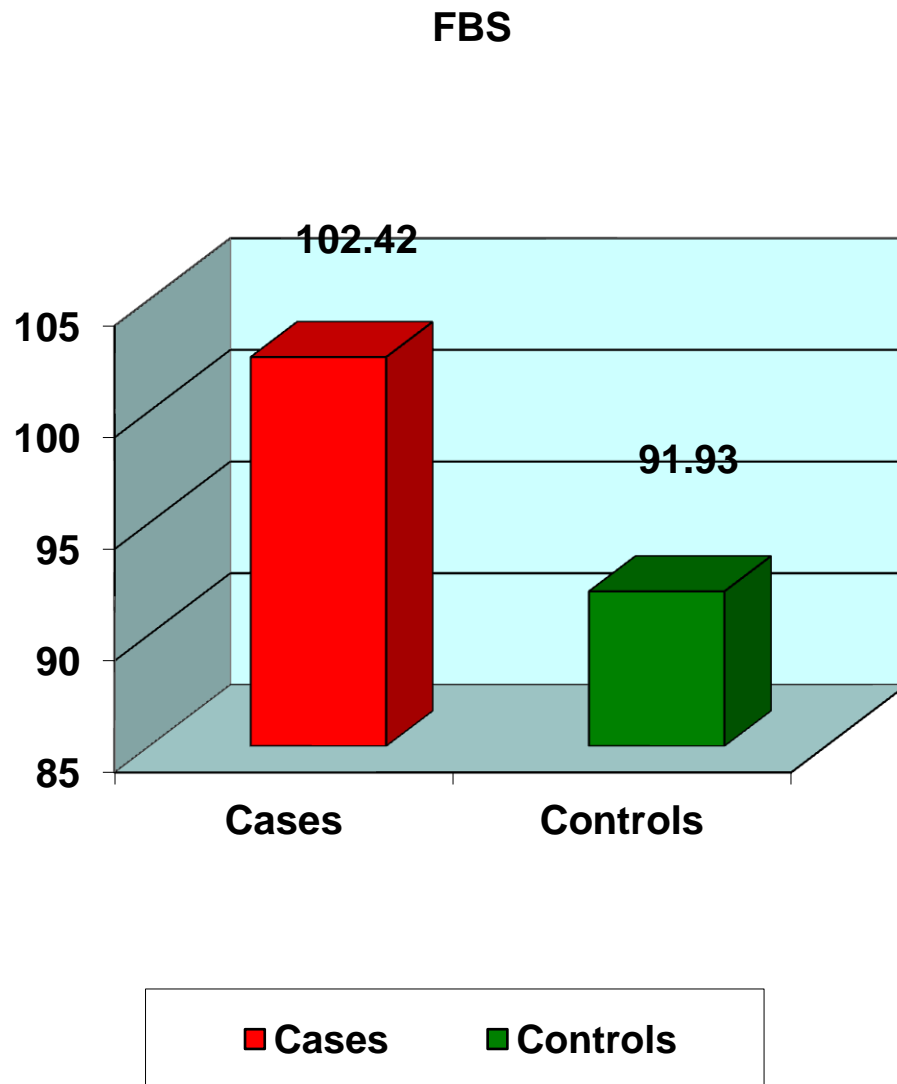
Table 4: MEAN PATTERN OF PPBS

PPBS(mg/dl)	Mean	SD	'p' value
Cases	187.02	30.59	<0.001
Controls	123.83	7.63	

The mean FBS level among cases and control were 102.42 ± 11.16 mg/dl and 91.93 ± 4.32 mg/dl respectively.

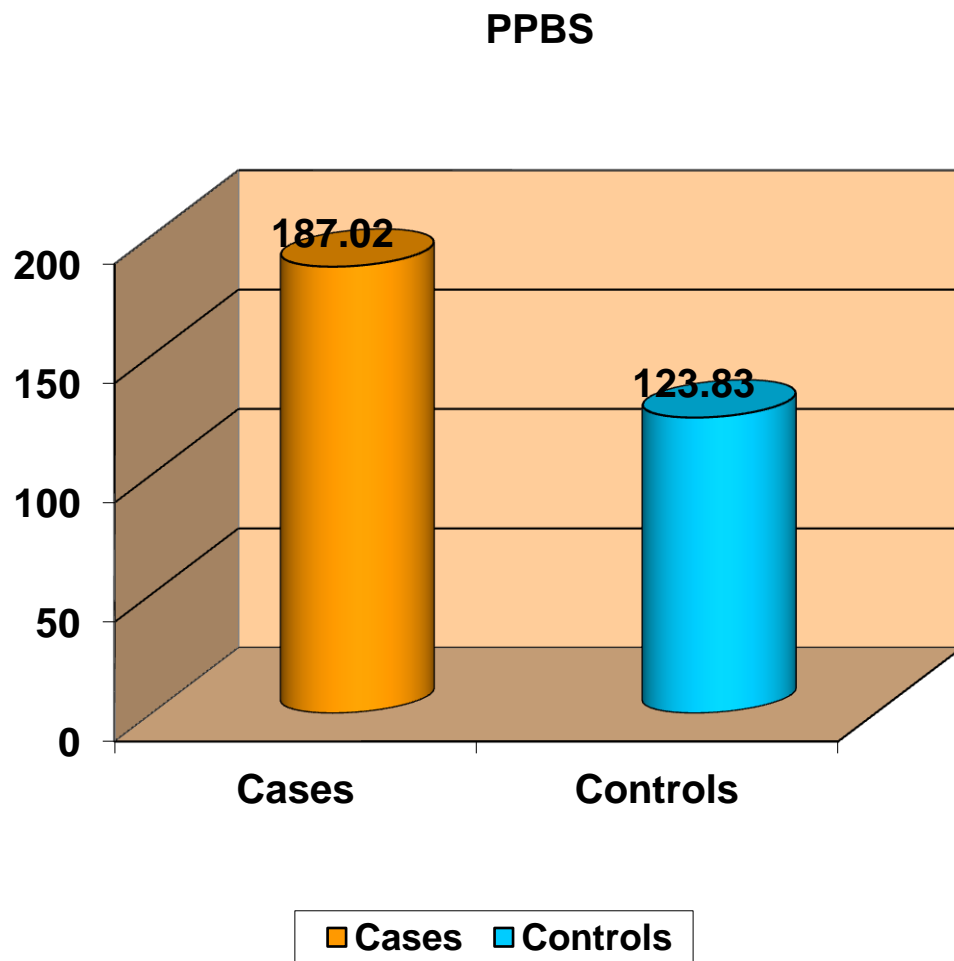
The mean PPBS level among cases and control were 187.02 ± 30.59 mg/dl and 123.83 ± 7.63 mg/dl respectively.

Figure 3: MEAN PATTERN OF FBS



The mean FBS level among cases and control were 102.42 ± 11.16 mg/dl and 91.93 ± 4.32 mg/dl respectively.

Figure 4: MEAN PATTERN OF PPBS



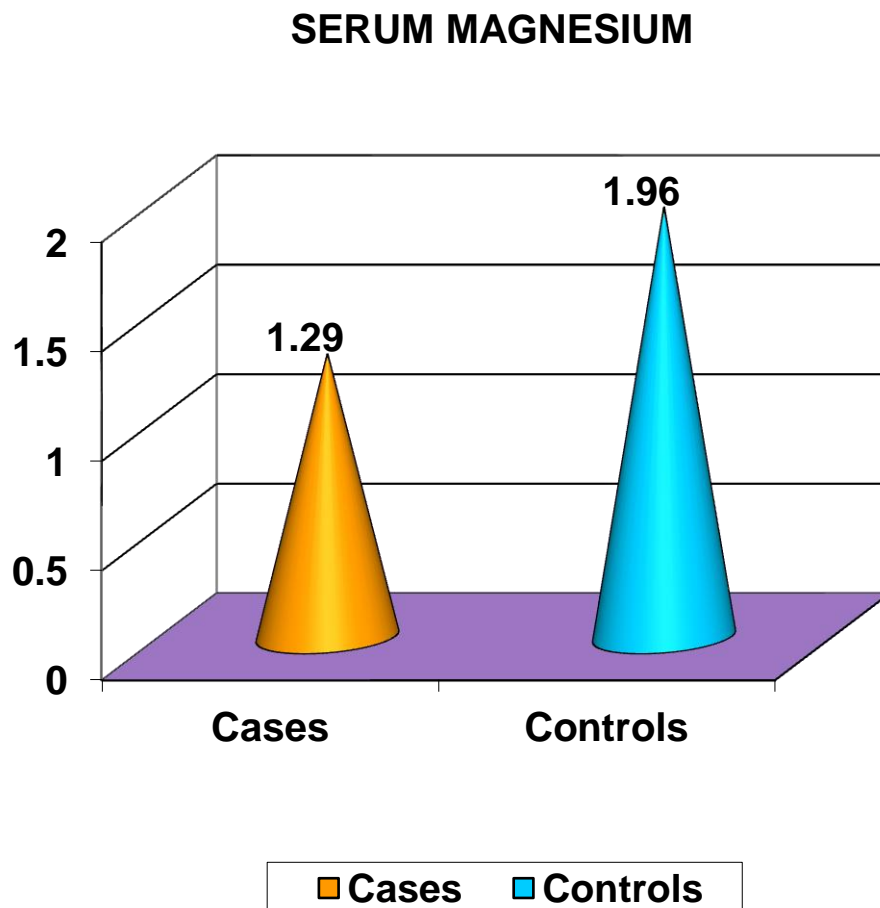
The mean PPBS level among cases and control were 187.02 ± 30.59 mg/dl and 123.83 ± 7.63 mg/dl respectively.

**Table 5: COMPARISON OF SERUM MAGNESIUM LEVEL
BETWEEN CASES AND CONTROLS**

Serum Magnesium(mEq/L)	Mean	SD	'p' value
Cases	1.29	0.42	<0.001
Controls	1.96	0.25	

There was significant difference between levels of serum magnesium levels among cases and controls. The mean serum magnesium levels of cases and controls were 1.29 ± 0.42 mEq/L and 1.96 ± 0.25 mEq/L respectively.

Figure 5: COMPARISON OF SERUM MAGNESIUM LEVEL BETWEEN CASES AND CONTROLS



The mean serum magnesium level in cases and controls were 1.29 ± 0.42 mEq/L and 1.96 ± 0.25 mEq/L respectively.

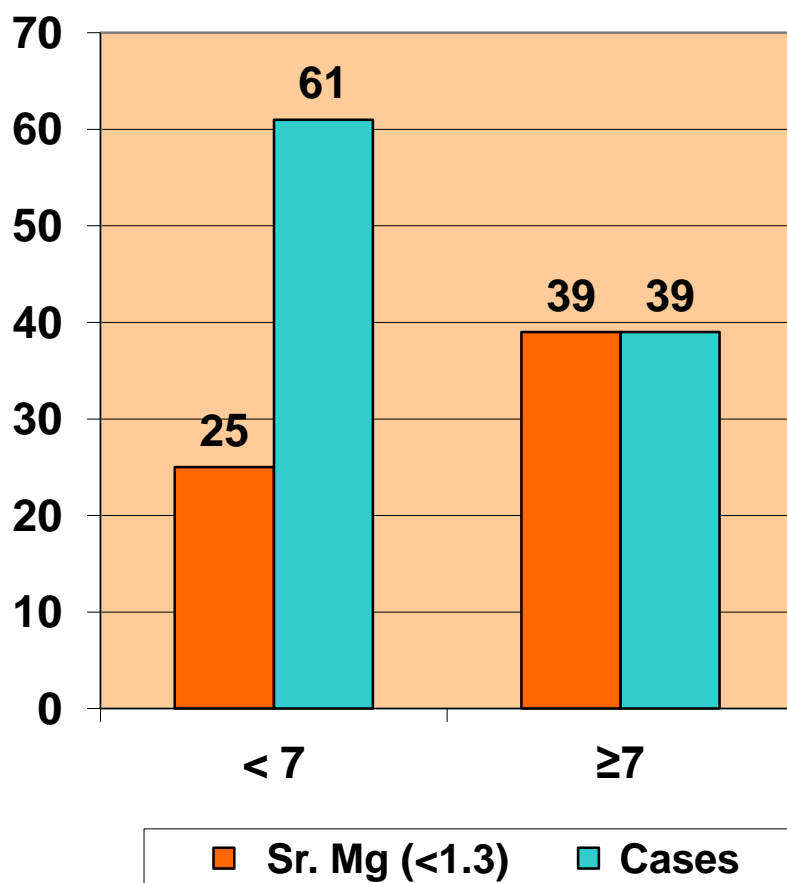
Table 6: COMPARISON OF SERUM MAGNESIUM LEVEL BETWEEN CONTROLLED AND UNCONTROLLED DIABETES

HbA1C(%)	Cases	Serum Magnesium level(< 1.3 mEq/L)	'p' value
< 7	61	25	0.01
≥ 7	39	39	

There was significant difference between magnesium levels among controlled and uncontrolled diabetics. Magnesium level was significantly lower in uncontrolled than that of controlled diabetics.

Figure 6:

**COMPARISON OF Sr.Mg IN CONTROLLED
AND UNCONTROLLED DIABETES**



Out of 61 cases with controlled diabetes ($\text{HbA1c} < 7$), 25 cases had low serum magnesium level. Out of 39 cases with uncontrolled diabetes ($\text{HbA1c} \geq 7$), 39 cases had low serum magnesium level. Based on chi-square test, serum magnesium is significantly ($p=0.01$) lower in uncontrolled than that of controlled diabetics. The mean serum magnesium levels of uncontrolled and controlled diabetic cases were

0.99±0.09 mEq/L and 1.48±0.42 mEq/L respectively. The difference was statistically significant based on standard error between two means.

Statistical methods:

Student T test has been used to find the significance of serum magnesium levels between cases and controls.

Chi – square test is used to find the significance of mean serum magnesium level among controlled and uncontrolled diabetics.

DISCUSSION

This study was conducted in Government Rajaji Hospital, Madurai in patients who were attending General Medicine Outpatient department. This study has enrolled a total of 100 cases and 100 healthy controls who were age and sex matched.

AGE DISTRIBUTION:

In the present study, the mean age group of cases and controls were 50.39 ± 9.76 and 50.01 ± 10.15 respectively. The minimum age was 31 years and maximum age was 70 years. Maximum number of patients are in the age group of 41 to 50 i.e., 42%.

In the study done by Maula MG et al conducted in 2013, the mean age of cases and controls were 48.08 and 47.74 years respectively and the total numbers of study subjects were 50.

In the study done by Shrabani Mohanty et al in Bangalore (2013), the mean age of cases and controls were 54.36 ± 11.25 and 51.81 ± 10.25 respectively and the total numbers of study subjects were 100. The mean age of diabetic population is 4th to 5th decade in the present as well as previous studies.

SEX DISTRIBUTION:

In this study, out of 100 cases, 70% were males and 30% were females.

In the study conducted by Maula MG et al²⁸ in 2013, among 50 cases, 58% were males and 42% were females. In the study conducted by Shrabani Mohanty et al in Bangalore (2013), among 100 cases 70% were males and 30% were females.

In the study conducted by Monika K et al in Switzerland, among 109 cases 70% were males and 30% were females.

SERUM MAGNESIUM IN DIABETICS AND CONTROLS:

In this study, the mean magnesium level in cases and controls were 1.29 ± 0.42 and 1.96 ± 0.25 and it is found to be significant ($p < 0.001$).

The study conducted by Shrabani Mohanty et al in Bangalore has shown that serum magnesium in diabetics (1.58 ± 0.28) is significantly lower ($p < 0.001$) when compared to controls (1.91 ± 0.22).

In the study conducted by Ashima Badyal et al in Haryana (2011), it is shown that serum magnesium level is significantly lower ($p < 0.001$) in diabetics (1.62 ± 0.47) when compared to healthy controls (2.33 ± 0.37).

In the study conducted by Nadler JL et al²⁹, the mean magnesium level in cases and controls were 1.94 ± 0.05 and 2.31 ± 0.12 respectively. This study shows that intracellular magnesium concentration in diabetics were significantly reduced when compared to controls and oral magnesium supplementation for 8 weeks restored RBC magnesium concentration to normal.

In the study conducted by Nagase N et al³⁰, serum magnesium level of diabetics (1.90 ± 0.37) was significantly lower than that of normal controls (2.30 ± 0.32).

In the study done by Maula MG et al in Rangpur, serum magnesium level in diabetics were significantly ($p < 0.001$) lower than that of healthy non diabetic subjects.

In the present study, serum magnesium is significantly lower ($p < 0.01$) in uncontrolled diabetics than that of controlled diabetics. In the study conducted by Nagase N in Japan, serum magnesium level of poorly controlled diabetics is lower than that of well controlled diabetics and this result suggest that magnesium deficient state is one of the cause of insulin resistance.

This study has focussed on assessing serum magnesium level at a given point of time among diabetic population and the level of

magnesium deficiency between controlled and uncontrolled diabetics. The study has shown that hypomagnesemia occurs in diabetes mellitus, and uncontrolled diabetics have lower level compared to controlled diabetics. Since magnesium is involved in various levels of insulin secretion, binding and activity, magnesium deficiency decreases insulin sensitivity which leads to raised blood sugar levels.

However in the present study, the amount of dietary intake of magnesium (a cause of hypomagnesemia) was not taken into consideration because of individual variations in dietary intake and magnesium metabolism. The evaluation of effects of oral/ IV magnesium towards metabolic control and complications of diabetes related to hypomagnesemia were not included in our study.

CONCLUSION

1. Serum magnesium levels were lower in type 2 diabetes patients when compared to healthy non-diabetic controls.
2. Levels of serum magnesium in uncontrolled type 2 diabetes were lower when compared to controlled diabetic patients.

Hypomagnesemia is one of the factors in type 2 diabetes which leads to various complications. Hence it is worthwhile to estimate serum magnesium level in type 2 diabetic patients and hypomagnesemia should be corrected to prevent insulin resistance and for better glycemic control.

SUMMARY

Estimation of serum magnesium level of 100 patients of type 2 diabetes and 100 healthy controls who attended OPD in Government Rajaji hospital, Madurai was done.

1. The mean age of cases and controls were 50.39 ± 9.76 and 50.01 ± 10.15 years respectively.
2. The maximum number of patients was in the age group of 41-50 (42%)
3. Among the cases and controls, the sex distribution were same i.e., 70% males and 30% females.
4. The mean FBS level among cases and control were 102.42 ± 11.16 mg/dl and 91.93 ± 4.32 mg/dl respectively.
5. The mean PPBS level among cases and control were 187.02 ± 30.59 mg/dl and 123.83 ± 7.63 mg/dl respectively.
6. The mean serum magnesium level in cases and controls were 1.29 ± 0.42 mEq/L and 1.96 ± 0.25 mEq/L respectively. i.e serum magnesium level among cases were significantly lower than controls.
7. Magnesium level was significantly lower in uncontrolled than that of controlled diabetics.

BIBLIOGRAPHY

1. Savis NEL, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A: Magnesium An update on physiological, clinical and analytical aspects. Clin Chem Acta 294: 1-26,2000
2. David BM. Tietz text book of clinical chemistry.2nd edition.W.B Saunders;1994
3. Rude RK, Singer FR. Magnesium deficiency and excess. Annu rev med 1981;32:245-259
4. Quamme G.A.Am J .Physiol.,1989,256, F197-F202
5. Elin RJ. Assessment of magnesium status. Clin chem. 1987;33:208
6. Elin RJ. Status of mononuclear blood cell magnesium assay. J Am Coll.Nutr 1987;6:1965-1975
7. Tabata M, Kido T, Murachi T. Direct spectrometry of magnesium in serum after reaction with hexokinase and glucose-6-phosphate dehydrogenase. Clin Chem 1985;31;703-705
8. Mastin MT, Shapiro R. Atomic absorption spectrometry of magnesium. Methods Enzymol 1988;158:365-370

9. Savory J, Margrey KS, Shipe JR, et al. Stabilization of calmagite reagent automated measurements of magnesium in serum and urine, Clin Chem 1985;31:487-488
10. Liedtke RJ, Kroon G. Automated calmagite compleximetric measurement of magnesium in serum with sequential addition of EGTA to eliminate endogenous interference. Clin Chem 1984;30:1801-1804
11. Barbour HM, Davidson W, studies on measurement of plasma magnesium: Application of Magon dye method to the monarch centrifugal analyzer. Clin Chem 1988;34:2103-2105
12. Burcar PJ, Boyle AJ, Mosher RE. Spectrometric determination of magnesium in blood using Magon. Clin Chem 1964;10:1028-1038
13. API text book of Medicine , 9th Edi, volume 1;237-238
14. Garfinkel D., magnesium ,1988,7,249-261
15. Baynes,J.W., Diabetes,1991;40:405-412
16. Resnick,L.M.Am.J.Hypertens.,1993;6;123:1S-134S
17. Zhou,Q., Mahfouz, M.M and Kummerow, F.A. Magnes Res., 1994, 7;23-30
18. Guyton and Hall: text book of medical physiology 11 Edi; 961-967
19. American Diabetes Association : Diagnosis and classification of diabetes mellitus. Diabetes care 31:555-560:2008

20. Griffin SJ, Little PS, Hales CN, Kinmonth AL, Wareham NJ;
diabetes risk score; toward earlier detection of type 2 diabetes in
general practice. *Diabetes Metab Res Rev* 16;164-171;2000
21. Barness LA, Opitz JM, Gilbert- Barnes E: obesity; genetic,
molecular, and environmental aspects. *Am F Med Genet A*
143:3016-3034,2007
22. Boden G: Pathogenesis of type 2 diabetes : insulin resistance.
Endocrinol Metab Clin North Am 30;801-825:2001
23. API textbook of Medicine, 9th edi,volume 1:333-334
24. Casey JJ; Host defence and infections in diabetes mellitus. In
Ellenberg and Rifkin's diabetes mellitus : Therapy and practice.3rd
edi; Ellenberg , Rifkin H, Eds New York ; Elsevier science, 1984
25. API textbook of Medicine, 9th edi, volume 1; 378-379
26. Ford ES, Giles WH. A comparison of prevalence of the metabolic
syndrome using two proposed definitions. *Diabetes Care*26(3);575-
581;2003
27. American Diabetes Association Guide to nutritional therapy for
diabetes 2nd edi. Franze M and Evert A, Eds.2012
28. *Dinajpur Med Col J* 2013;jul; 6(2); 123-127

29. Nadler JL, Malayan S, Luong H, Shaw S, Natrajan RD, Ruke RK.

Intracellular magnesium deficiency plays a key role in increased platelet reactivity in type 2 diabetes mellitus; Diabetic Care 1992; 15; 835-841

30. Nagase N, Hypertension and serum magnesium in patients with diabetes and coronary artery disease. Hypertens Res 1996; 19; 65-68.

PROFORMA

Name: **Age/Sex:** **Occupation:**

Presenting illness:

H/O polyuria, polyphagia, polydipsia, chestpain, sweating, paresthesia, blurring of vision, breathlessness, swelling of legs, fatiguability.

Past history:

H/O smoking, alcohol, hypertension, diabetes, heart disease, ESRD, thyroid disease, gout.

Drug history:

Family history:

Clinical examination:

General examination:

Vitals: Pulse rate:

Blood pressure:

Systemic examination: CVS:

RS:

ABDOMEN:

CNS:

LABORATORY INVESTIGATIONS:

1. Fasting blood glucose
2. Postprandial blood glucose
3. Serum magnesium
4. HbA1c
5. Serum urea and creatinine
6. Urine analysis
7. ECG

ABBREVIATIONS

EGTA - Ethylene Glycol- O,O- bis(2- aminoethyl) N,N Tetra Acetic acid

ATP – Adenosine Tri Phosphate

TRPM - Transient Receptor Potential channel Melastatin member

KCN - potassium cyanide

ER- Endoplasmic Reticulum

PP Cell- Pancreatic Polypeptide cell

CoA - coenzyme A

VLDL - Very Low Density Lipoprotein

HDL – High Density Lipoprotein

LDL – Low Density Lipoprotein

GLP - Glucagon Like Peptide

GIP - Glucose dependent Insulinotropic Peptide

GLUT – Glucose Transporter

PPAR- γ -Peroxisome Proliferator Activated Receptor-Gamma

MODY- Maturity Onset Diabetes of the Young

FFA - Free Fatty Acid

eGFR- Estimated Glomerular Filtration Rate

Spot PCR – Spot Protein Creatinine Ratio

ADA- American Diabetes Association

Mg – Magnesium

mg – milligram

mEq/L –milli Equivalents per litre

BMI – Body Mass Index

GDM – Gestational Diabetes Mellitus

OGTT – Oral Glucose Tolerance Test

MASTER CHART-CASES

S.NO	CASES	AGE (years)	SEX	OP.NO	FBS (mg/dl)	PPBS (mg/dl)	Sr.Mg (meq/L)	HbA1c (%)	UREA (mg/dl)	CREATININE (mg/dl)
1	RAMASAMY	32	M	61648	110	213	1.1	7.2	28	0.9
2	PALANISAMY	41	M	66144	110	210	1.1	7.2	19	0.9
3	PITACHAI	46	M	59219	96	170	1.5	6.1	26	1.1
4	PUSHPARAJ	38	M	57114	110	241	1	7.4	18	1.1
5	PALANI	49	M	66999	98	172	1.9	6	24	1
6	RAMASAMY	44	M	65111	120	198	1	7.1	20	1
7	PODHUMPONNU	40	F	55144	92	119	1	6.3	22	0.9
8	MARUTHUPANDI	47	M	59229	88	174	2	6.1	28	1.1
9	ARUN	32	M	72646	98	124	1.1	6.4	21	0.9
10	SELVI	44	F	59325	115	120	1	7.1	27	0.8
11	THENNARASU	34	M	54114	90	116	1.9	6.3	21	1
12	MUTHU	52	M	67100	110	230	1.1	7.1	29	0.9
13	CHELLADURAI	45	M	65122	90	180	2.1	6.3	26	0.9
14	PATTAMMAL	42	F	65655	126	211	1	7.3	20	0.7
15	PALANIAPPAN	52	M	60001	114	210	1	7.9	28	0.9
16	KALIAMMAL	57	F	62211	92	190	2	6.7	32	0.7
17	ALAGAR	42	M	59420	121	240	1	7.6	20	1
18	PALANI	64	M	67599	114	207	1.1	7.1	28	0.9
19	SIVAKAMI	45	F	59383	114	206	0.9	7.5	18	0.8
20	SAMIKANNU	70	M	66651	110	210	1	7.3	29	0.9
21	ANBU	45	M	58114	114	220	0.9	7.4	18	0.9
22	RAKAYI	53	F	66953	94	176	1.9	6.5	29	0.8
23	CHELLAPPAN	69	M	65555	124	220	0.9	7.4	30	0.9
24	MANI	44	M	59114	116	219	0.8	7.5	22	0.8
25	CHELLAPPAN	50	M	59211	92	190	1.9	6.2	24	0.8
26	MOHAMMAD	43	M	66818	91	182	1.8	6.3	23	1.1
27	CHINNAKANNU	46	F	59309	124	204	1.1	7.2	25	0.9
28	DURAIPANDI	68	M	65656	110	209	0.9	7.5	25	0.8
29	RAMASAMY	69	M	67515	107	217	1	7.2	26	0.7
30	SURULAI	65	M	65566	110	212	0.9	7.4	28	0.8
31	MARIAPPAN	39	M	68104	99	122	2.1	6.5	19	0.7
32	PALANISAMY	39	M	61414	96	110	0.8	6.5	25	0.8
33	ALAGAR	64	M	61742	114	232	1	7.5	29	1
34	KANNAPPAN	68	M	67611	90	184	1	6.2	30	0.9
35	CHINNASAMY	62	M	66078	92	192	0.9	6.3	29	0.9
36	NAGARAJ	43	M	59419	114	211	1.1	7.2	20	0.9
37	PARVATHI	51	F	67391	97	184	1.8	6.6	28	0.9

38	PALANISAMY	63	M	61182	96	180	1.1	6.1	30	0.7
39	NALLU	46	M	66214	115	210	1.2	7.1	18	0.9
40	FATHIMA	54	F	60193	98	171	1	6.4	28	1.1
41	CHINNADEVAR	64	M	67680	90	192	1.8	6.6	28	0.8
42	PANDI	65	M	60968	92	190	1.9	6.5	24	0.9
43	MALLIKA	52	F	63466	96	180	1.6	6.5	24	0.8
44	VEERANAN	42	M	58314	110	211	1	7.2	22	1
45	CHAKRAVARTHI	64	M	61977	94	182	1.8	6.5	26	0.9
46	LAKSHMI	53	F	67390	112	209	0.9	7.4	24	1
47	MUTHUSAMY	35	M	60414	124	209	0.9	7.4	20	1
48	MANI	39	M	54318	114	250	1.1	7.6	19	0.8
49	JANAKI	59	F	60899	116	211	0.9	7.3	27	0.8
50	PITACHAI	44	M	58240	112	230	1	7.4	24	0.9
51	MARUTHU	63	M	67622	92	180	2	6.4	28	1
52	ANJALAI	44	F	59159	99	180	2.1	6.5	24	0.9
53	MANIKANKAN	64	M	63455	91	180	2.1	6.5	30	0.9
54	PONNUTHAI	65	F	69154	121	211	1.2	7.5	32	0.8
55	CHANDRAN	41	M	54110	114	241	1	7.6	22	0.9
56	KANNATHAL	62	F	67810	96	190	1.1	6.2	28	0.7
57	PONNUTHAI	45	F	66149	98	172	1.9	6.5	24	1
58	VALLI	63	F	69213	82	160	1	6.6	24	0.9
59	SORNALAKSHMI	59	F	63291	114	207	1	7.1	26	0.9
60	RAVI	50	M	58119	96	168	1.1	6.8	26	0.9
61	ALAGI	66	F	65188	94	162	2.1	6.5	29	0.8
62	KALIAMMAL	49	F	59166	84	174	1.8	6.4	22	0.9
63	CHINNAKANNU	67	F	67911	90	174	1.9	6.1	18	0.7
64	KANNATHAL	55	F	67311	112	210	1.1	7.2	24	0.8
65	CHINNAKANNU	45	M	66333	100	188	1.1	6.6	24	1
66	MOOKAMMAL	50	F	66577	98	176	1	6.5	23	1
67	BASKARAN	50	M	65144	94	190	1.2	6.3	28	0.8
68	PANDIDURAI	54	M	61199	93	176	1.5	6.5	25	0.7
69	PALANI	43	F	65844	94	174	0.9	6.4	24	1.1
70	MANI	53	M	61114	94	174	1.6	6.6	28	0.8
71	RAMU	37	M	56008	92	198	1.1	7.5	21	1
72	PAULSAMY	38	M	71438	120	211	0.9	7.3	24	0.9
73	ESWARAN	49	M	58746	96	176	1	6.5	22	0.9
74	PANDIAMMAL	41	F	59911	93	163	1.5	6.4	21	1
75	KALIAPPAN	56	M	63390	96	180	2	6.5	29	0.9
76	KASILINGAM	54	M	67292	112	182	1.6	6.5	28	1
77	SORNAM	42	F	59529	99	182	1	6.7	24	0.9
78	PALANI	53	M	63311	120	184	1	6.4	29	0.9
79	GANDHI	46	M	59698	98	174	1	6.5	30	0.8
80	KANDASAMY	53	M	60333	110	176	1.1	6.5	30	0.8
81	MASANAM	55	M	61057	94	193	1.8	6.8	18	0.9

82	PANDI	53	M	60157	106	174	0.9	6.3	29	0.9
83	LAKSHMANAN	48	M	66414	94	180	1.1	6.4	28	1
84	VALLI	45	F	65711	92	140	1.1	6.9	27	0.7
85	ALAGARSAMY	35	M	71111	82	120	1.4	6.1	26	0.8
86	PARVATHI	42	F	65629	96	176	2	6.3	21	0.8
87	PANDI	47	M	58818	98	162	1.1	6.3	24	1
88	VEERANAN	60	M	67201	110	227	1	7.4	25	0.7
89	MUTHUMARI	52	M	61005	114	200	1.1	6.5	27	0.8
90	PALANI	49	M	59147	92	188	1.5	6.5	30	0.8
91	MARUTHU	59	M	60096	116	220	0.9	7.4	27	0.9
92	MAIDEEN	59	M	60156	110	240	0.9	7.2	28	1
93	ALAGU	47	M	66800	91	180	1.6	6.7	24	0.9
94	KARUTHAPPAN	59	M	63201	112	211	1	7.2	25	1
95	YOGALAKSHMI	49	F	59591	89	156	0.9	6.8	26	0.8
96	PANDI	33	M	62114	92	124	2	6.3	28	0.9
97	KURALARASU	37	M	66111	94	110	1.8	6.4	19	0.8
98	RAGHURAM	48	M	59289	94	170	1.7	6.6	26	0.8
99	RAJA	48	M	65221	93	164	1.6	6.2	18	0.7
100	SARASU	43	F	66888	110	204	0.8	7.4	24	0.9

MASTER CHART-CONTROLS

S.NO	CONTROLS	AGE (years)	SEX	OP.NO	FBS (mg/dl)	PPBS (mg/dl)	Sr.Mg (mEq/L)	UREA (mg/dl)	CREATININE (mg/dl)
1	NARAYANAN	31	M	69111	92	142	2	38	0.9
2	VELLADURAI	45	M	69141	85	124	1.8	33	1
3	SATHISH	47	M	70124	93	116	2.2	28	0.9
4	SIVANESAN	48	M	65655	92	120	2	37	0.8
5	LAKSHMI	42	F	68433	81	125	2.3	24	0.9
6	RAMAYEE	50	F	69555	96	124	2	29	0.8
7	SENBAGARAM	44	M	69161	88	120	1.8	34	1
8	VEERAPANDI	48	M	70001	96	126	2.1	38	0.8
9	GANAPATHY	36	M	70199	90	136	2.1	28	1
10	PERIYAKARUPPAN	44	M	69911	84	127	1.8	30	0.9
11	VANI	41	F	68444	99	129	1.9	30	0.7
12	SIVA	41	M	69961	93	122	2.1	30	1
13	MUTHUKUMAR	53	M	70818	95	124	2	28	0.8
14	RAMAKRISHNAN	54	M	71600	93	122	1.8	30	0.9
15	KARMEGAM	32	M	71462	91	140	1.5	24	0.8
16	MEENAKSHI	44	F	69182	87	123	2.4	28	1
17	MANI	59	M	70707	96	119	2.2	32	0.7
18	SHENBAGALINGAM	47	M	69653	86	119	2	33	0.9
19	ARUMUGAM	48	M	69524	94	120	2	31	0.9
20	MARANAADU	54	M	71706	92	124	2	32	1
21	MAAYI	45	M	69143	87	119	2.4	35	0.9
22	SUNDARAVADIVU	46	F	71432	97	126	1.8	30	0.9
23	ILAYARAJA	32	M	69948	82	141	2	29	0.8
24	IYYANAR	54	M	70806	96	121	1.9	24	0.9
25	VELMURUGAN	58	M	69816	95	124	2.3	29	0.7
26	GNANAPANDI	55	M	68909	94	122	2.1	30	0.9
27	SANKARALINGAM	50	M	69151	94	130	1.9	36	0.8
28	RAVI	55	M	67514	96	124	2	28	1
29	PAPATHI	55	F	63314	96	121	1.9	34	0.9
30	RAMAR	46	M	70424	91	120	2	28	1
31	KRISHNAN	57	M	68814	95	121	2.4	30	0.7
32	MARUTHALINGAM	46	M	69513	92	129	2.3	34	1
33	NAATUDURAI	56	M	69514	93	119	1.8	33	1
34	RANGARAJAN	31	M	69698	98	142	1.6	29	1.1
35	KATHIRESAN	57	M	68414	92	119	1.7	38	1
36	VANI	54	F	66844	99	124	1.8	28	1

37	KRISHNA	49	M	70411	95	124	2	29	0.9
38	KAALI	56	F	73806	88	119	1.8	30	1
39	MARUTHAMUTHU	37	M	68924	96	148	2.2	28	1
40	NATARAJAN	47	M	70015	97	128	2.1	32	1
41	GOMATHI	45	F	66411	88	128	2.1	29	0.8
42	VALARMATHI	58	F	73414	98	122	1.8	27	1
43	KALIMUTHU	43	M	70142	83	125	2.2	29	0.8
44	KALAIVANI	53	F	73916	82	121	1.7	32	0.7
45	BAKKIYAM	64	F	71666	89	118	2.1	38	0.9
46	VALLI	44	F	71163	98	122	1.7	32	0.9
47	SUBRAMANI	49	M	70086	95	124	1.9	30	1
48	PARANTHAMAN	46	M	69181	98	120	2	31	1
49	KALIAMMAL	69	F	72142	89	124	2	38	1
50	PATCHAIAMMAL	70	F	70809	95	126	1.9	30	0.9
51	MACHAKAALAI	33	M	70611	93	142	2.1	25	0.8
52	PAPATHI	59	F	74866	86	119	1.9	34	0.9
53	PETCHI	65	F	71717	92	124	1.8	34	1
54	SARASWATHI	47	F	71086	96	124	2.4	22	0.8
55	PONRAJ	38	M	71423	86	141	2.3	30	0.9
56	VEERAMMAL	68	F	73866	94	110	1.9	37	1
57	THANGAVEL	33	M	69121	92	136	1.7	29	0.7
58	RANGARAJAN	64	M	74711	88	118	2.2	33	0.9
59	PARVATHI	43	F	70177	92	128	1.8	38	1
60	RAJU	34	M	70092	94	124	2.2	30	0.8
61	ARUMUGAM	69	M	71724	95	124	1.9	34	1
62	PERIANNAN	64	M	70539	89	110	1.8	34	1
63	RAMALAKSHMI	48	F	73486	83	121	2	26	1
64	MAHALINGAM	63	M	68333	92	124	2	36	0.9
65	SREENIVASAN	62	M	69811	92	126	1.9	34	1
66	RAMU	39	M	71091	88	116	2.4	26	0.9
67	LATHA	43	F	69146	95	123	2.3	27	0.8
68	SUBBAIAH	68	M	66196	95	120	1.8	28	0.9
69	MURUGAVEL	63	M	67320	88	114	1.4	32	0.7
70	PARASURAM	66	M	66194	92	112	1.3	36	1
71	KANNAN	34	M	72209	95	151	1.8	28	1
72	SELVAM	67	M	67279	89	108	1.6	34	1
73	MANI	35	M	69131	97	132	2.3	31	0.9
74	MALLIGA	42	F	69999	94	130	2.2	24	0.9
75	SEKAR	64	M	68978	94	112	1.4	30	0.9
76	BABULAL	62	M	69455	95	116	1.3	38	0.9
77	KRISHNAN	40	M	72609	87	126	2.5	27	0.7
78	THAIYALNAYAGI	49	F	68941	92	123	1.9	28	1
79	VALLI	36	F	71142	89	122	1.9	32	0.8
80	KALAI	42	F	66933	88	128	2.1	30	1

81	MALAISAMY	66	M	74837	94	124	1.4	37	0.9
82	SUBBURAJ	41	M	69616	91	128	1.6	38	0.9
83	AIYYAVU	60	M	71446	92	121	2.1	29	0.7
84	PERUMAL	63	M	71113	92	114	1.8	32	0.9
85	DHANDAPANI	50	M	69572	98	130	2.3	39	0.8
86	KARUPAAYEE	41	F	63846	88	121	2	28	0.9
87	MURUGAN	61	M	70846	95	116	1.9	38	0.7
88	MUNUSAMY	42	M	69174	89	124	2.1	23	1
89	MARIAMMAL	60	F	72149	95	122	1.9	34	1
90	ALAGU	55	M	68913	95	118	2.2	28	0.9
91	ADAIKAN	43	M	69544	99	120	2.2	32	0.9
92	KANNATHAL	51	F	72243	91	118	1.7	29	0.9
93	MARI	49	M	69171	100	118	1.7	35	0.7
94	MAHALINGAM	51	M	71888	88	121	1.9	30	1
95	RAJENDRAN	52	M	68841	91	122	1.9	29	0.9
96	JAYAPAL	53	M	69814	84	124	2	38	0.9
97	BOSE	43	M	69511	90	121	2.1	32	1
98	PALANIAMMAL	52	F	73343	90	126	1.8	30	1
99	RAMALINGAM	51	M	69743	92	119	2.2	30	0.7
100	SOLAI	42	M	69575	86	119	2	33	1

ETHICAL COMMITTEE APPROVAL LETTER

Ref.No.6506/E1/5/2014

Madurai Medical College,
Madurai -20. Dated: 31.07.2014.

Institutional Review Board/Independent Ethics Committee
Capt.Dr.B.Santhakumar,MD (FM). deanmdu@gmail.com
Dean, Madurai Medical College &
Government Rajaji Hospital, Madurai 625 020 . Convenor

Sub: Establishment – Madurai Medical College, Madurai-20 –
Ethics Committee Meeting – Meeting Minutes - for July 2014 –
Approved list – reg.

The Ethics Committee meeting of the Madurai Medical College, Madurai was held on 22nd July 2014 at 10.00 Am to 12.00 Noon at Anaesthesia Seminar Hall at Govt. Rajaji Hospital, Madurai . The following members of the Ethics Committee have attended the meeting.

- | | | |
|--|--|---------------------|
| 1.Dr.V.Nagarajan,M.D.,D.M(Neuro)
Ph: 0452-2629629
Cell No.9843052029
nag9999@gmail.com . | Professor of Neurology
(Retired)
D.No.72, Vakkil New Street,
Simmakkal, Madurai -1 | Chairman |
| 2.Dr.Mohan Prasad, MS.M.Ch.
Cell.No.9843050822 (Oncology)
drbkemp@gmail.com | Professor & H.O.D of Surgical
Oncology (Retired)
D.No.32, West Avani Moola Street,
Madurai.-1 | Member
Secretary |
| 3. Dr.L.Santhanalakshmi, MD (Physiology)
Cell No.9842593412
dr.l.santhanalakshmi@gmail.com . | Vice Principal, Prof. & H.O.D.
Institute of Physiology
Madurai Medical College | Member |
| 4.Dr.K.Parameswari, MD(Pharmacology)
Cell No.9994026056
drparameswari@yahoo.com . | Director of Pharmacology
Madurai Medical College. | Member |
| 5.Dr.S.Vadivel Murugan, MD.,
(Gen.Medicine)
Cell No.9566543048
svadivelmurugan_2007@rediffmail.com . | Professor & H.O.D of Medicine
Madurai Medical College | Member |
| 6.Dr.A.Sankaramahalingam, MS.,
(Gen. Surgery)
Cell.No.9443367312
chandrahospitalmdu@gmail.com | Professor & H.O.D. Surgery
Madurai Medical College. | Member |
| 7.Mrs.Mercy Immaculate
Rubalatha, M.A., Med.,
Cell.No.9367792650
lathadevadoss86@gmail.com | 50/5, Corporation Officer's
Quarters, Gandhi Museum Road,
Thamukam, Madurai-20. | Member |
| 8.Thiru.Pala.Ramasamy, B.A.,B.L.,
Cell.No.9842165127
palaramasamy2011@gmail.com | Advocate,
D.No.72,Palam Station Road,
Sellur, Madurai-20. | Member |
| 9.Thiru.P.K.M.Chelliah, B.A.,
Cell No.9894349599
pkmandco@gmail.com | Businessman,
21 Jawahar Street,
Gandhi Nagar, Madurai-20. | Member |

The following project was approved by the committee


Name of the PG Student	Course	Name of the Project	Remarks
Dr.V.Praveen Praveencmc2004@gmail.com	PG in MD (General Medicine) Madurai Medical College & Rajaji Hospital, Madurai	A study of serum magnesium level in patients with type 2 diabetes mellitus	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain it confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution or to Government.
2. She/He should inform the institution Ethical Committee, in case of any change of study procedure, site and investigation or guide.
3. She/He should not deviate the area of the work for which applied for Ethical clearance.
She/He should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
4. She/He should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and if any extension of time is required He/She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on completion of the work.
7. She/He should not claim any funds from the institution while doing the work or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.


Member Secretary
Ethical Committee


Chairman
Ethical committee


31.7.14
DEAN/Convenor
Madurai Medical College & Govt.
Rajaji Hospital, Madurai.

To
The above Applicant
-thro. Head of the Department concerned



Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author: 201211111.md General Medicine PR...
Assignment title: TNMGRMU EXAMINATIONS
Submission title: A STUDY OF SERUM MAGNESIUM...
File name: thesis_full_copy.docx
File size: 942.04K
Page count: 114
Word count: 11,311
Character count: 66,434
Submission date: 21-Sep-2014 04:22PM
Submission ID: 452902228

**A STUDY OF SERUM MAGNESIUM LEVEL IN
PATIENTS WITH TYPE 2 DIABETES MELLITUS**

Dissertation submitted for

Branch I – MD (GENERAL MEDICINE)

April 2015



THE TAMILNADU Dr. M.G.R. MEDICAL
UNIVERSITY, CHENNAI, TAMILNADU.